SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CSA054886

Organizacion y
Digitalizacion CSA Ltda

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. **EXPEDIENTE No.** 08-12251

54. **TITULO** *NOVEDOSOS ANÁLOGOS DE PIRIDINA*

51. **CLASIFICACION INTERNACIONAL** A61K 31/4427; C07D 401/04 401/14, 413/14; A61P 7/02.

71. **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SÖDERTALJE, SUECIA

74. **APODERADO** JUAN PABLO CADENA SARMIENTO

22. **SANTAFE DE BOGOTA, D.C.**

PETITORIO

AS: 105.952

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-012251- -00000-0000
Fecha: 2008-02-07 16:43:01 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 672

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

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

☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: S-1-51 85 Södertalje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail:	**IDENTIFICACIÓN** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia. Teléfono: 744-2200 Fax: 742-2200 E-mail:	**IDENTIFICACIÓN** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	**Nombre**: Sören ANDERSEN, Peter BACH, Kay BRICKMANN, Fabrizio GIORDANETTO, Fredrik ZETTERBERG, Krister ÖSTERLUND. **Dirección:** AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE (Respectivamente). **Nacionalidad o Domicilio**: Suecia (Respectivamente).	

5 PCT (86)

Solicitud Internacional No. PCT/SE2006/000832 Fecha 04-07-2006
Publicación Internacional No. WO 2007/008140 A1 Fecha 18-01-2007

6 Título (54): NOVEDOSOS ANÁLOGOS DE PIRIDINA

7 Clasificación Internacional (51): C07D 401/04; A61K 31/4422; A61P 7/02; C07D 401/14, 413/14

8 Prioridad SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SE	13-07-2005	0501663-9
SE	24-10-2005	0502354-4

9 Comprobante de pago No: 07-104;568 08-705 **Fecha** 07-02-2008

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. $501.000
- [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
  Tarjeta de Propietarios
  Documentos PCT

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.

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

AS 105952

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 104,568
FECHA : DICIEMBRE 26 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-012251- -00000-0000
Fecha: 2008-02-07 16:43:01 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 672

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	64227007	24/12/2007	22,202,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

MEV

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/SE2006/000832 MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES ASTRAZENECA AB

DOMICILIO SÖDERTALJE, SUECIA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO NOVEDOSOS ANÁLOGOS DE PIRIDINA

CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) SÖREN ANDERSEN, PETER BACH, KAY BRICKMANN, FABRIZIO GIORDANETTO, FREDRIK

OTROS ZETTERBERG, KRISTER ÖSTERLUND.

OFICINA DE COMUNICACIONES

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMÁTICO

PATENTE DE INVENCIÓN _X_ PCT _X_ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

(21) No. de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional :

(71)Solicitante(s): ASTRAZENECA AB

(72) Inventor (es): Sören ANDERSEN, Peter BACH, Kay BRICKMANN, Fabrizio GIORDANETTO, Fredrik ZETTERBERG, Krister ÖSTERLUND.

(74) Agente: JUAN PABLO CADENA SARMIENTO

(30) Prioridad	(31) No. Prioridad	(32 Fecha	(33) País
	0501663-9	13-07-2005	SE
	0502354-4	24-10-2005	SE

(85) Fecha inicio fase nacional: 13-02-2008

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 04-07-2006
No. de solicitud: PCT/SE2006/000832

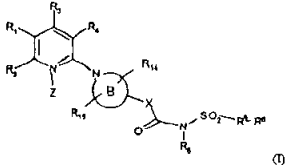
(87) Publicación internacional:
Fecha: 18-01-2007
No. Publicación: WO 2007/008140 A1

FIGURA CARACTERÍSTICA
6 x 6 cm

(54) Titulo: NOVEDOSOS ANÁLOGOS DE PIRIDINA

(55) Reivindicación(es):

1. Un compuesto de fórmula I o su sal farmacéuticamente aceptable:

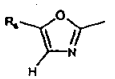


(I)

CONTINUA AL RESPALDO ...

en donde

R_1 representa $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ o un grupo gH



(gII),

R_2 representa H, CN, halógeno (F, Cl, Br, I), NO_2, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_{12})alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil (C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(2)}R^{b(2)}$ en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Además, R_1 + R_2 juntos (con dos átomos de carbono del anillo piperidina) pueden formar una lactona cíclica de 5 ó 6 miembros;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_{12})alquilo, interrumpido opcionalmente por oxigeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I);

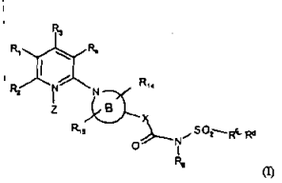
Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(1) No. de solicitud: (22) Fecha de solicitud: (30) Prioridad (31) No. Prioridad (32) Fecha (33) País 0501663-9 13-07-2005 SE 0502354-4 24-10-2005 SE	(51) Int Cl: (71) Solicitante (s): ASTRAZENECA AB (72) Inventor(es): Sören ANDERSEN, Peter BACH, Kay BRICKMANN, Fabrizio GIORDANETTO, Fredrik ZETTERBERG, Krister ÖSTERLUND. (74) Agente: JUAN PABLO CADENA SARMIENTO
(85) (85) Fecha inicio fase nacional: 13-02-2008 (86) Datos relativos a la presentación de la solic. PCT Fecha de presentación de la solicitud: 04-07-2006 No. de solicitud: PCT/SE2006/000832	(87) Publicación internacional Fecha: 18-01-2007 No. publicación: WO 2007/008140 A1
(54) Titulo: NOVEDOSOS ANÁLOGOS DE PIRIDINA	

(55) Reivindicación(es):

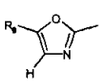
1. Un compuesto de fórmula I o su sal farmacéuticamente aceptable:



(I)

en donde

R_1 representa $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ o un grupo gH



(gII),

R_2 representa H, CN, halógeno (F, Cl, Br, I), NO_2, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxigeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_{12})alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1- C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil (C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(2)}R^{b(2)}$ en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Además, R_1 + R_2 juntos (con dos átomos de carbono del anillo piperidina) pueden formar una lactona cíclica de 5 ó 6 miembros;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_{12})alquilo, interrumpido opcionalmente por oxigeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I);

105752

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau

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(51) International Patent Classification:
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A61K 31/4427 (2006.01) *C07D 401/14* (2006.01)
A61K 31/4439 (2006.01) *C07D 413/14* (2006.01)
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0501663-9 13 July 2005 (13.07.2005) SE
0502354-4 24 October 2005 (24.10.2005) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANDERSEN, Sören** [DK/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **BACH, Peter** [DK/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **BRICKMANN, Kay** [DE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **GIORDANETTO, Fabrizio** [IT/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **ZETTERBERG, Fredrik** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **ÖSTERLUND, Krister** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

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

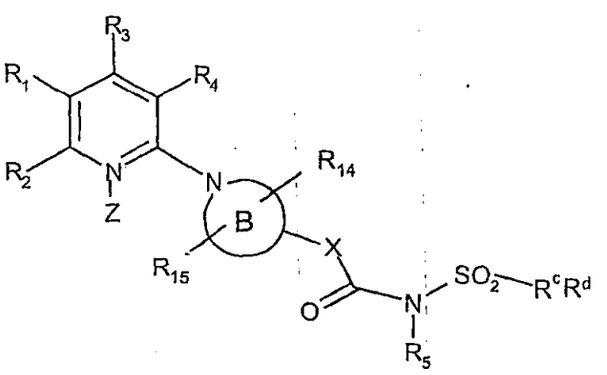
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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

(54) Title: NEW PYRIDINE ANALOGUES



(I)

(57) Abstract: The present invention relates to certain new pyridin analogues of Formula (I) Chemical formula should be inserted here. Please see paper copy Formula (I) to processes for preparing such compounds, to their utility as $P2Y_{12}$ inhibitors and as anti-trombotic agents etc, their use as medicaments in cardiovascular diseases as well as pharmaceutical compositions containing them.

WO 2007/008140 A1

NEW PYRIDINE ANALOGUES

Field of the invention

The present invention provides novel pyridine compounds, their use as medicaments, compositions containing them and processes for their preparation.

Background of the invention

Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

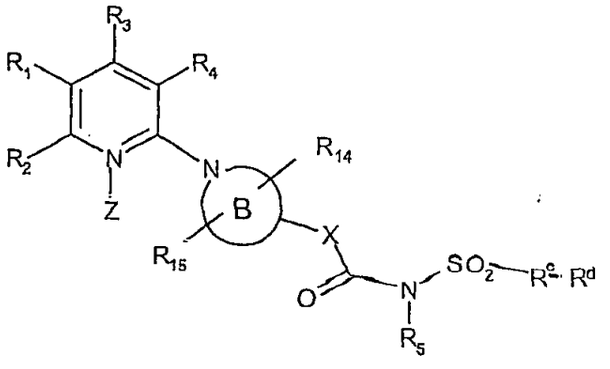
Haemostasis is controlled via a tight balance between platelet aggregation, coagulation and fibrinolysis. Thrombus formation under pathological conditions, like *e.g.* arteriosclerotic plaque rupture, is firstly initiated by platelet adhesion, activation and aggregation. This results not only in the formation of a platelet plug but also in the exposure of negatively charged phospholipids on the outer platelet membrane promoting blood coagulation. Inhibition of the build-up of the initial platelet plug would be expected to reduce thrombus formation and reduce the number of cardiovascular events as was demonstrated by the anti-thrombotic effect of e.g. Aspirin (BMJ 1994; 308: 81-106 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients). Platelet activation/aggregation can be induced by a variety of different agonists. However, distinct intracellular signalling pathways have to be activated to obtain full platelet aggregation, mediated via G-proteins G_q, $G_{12/13}$ and G_i (Platelets, AD Michelson ed., Elsevier Science 2002, ISBN 0-12-493951-1; 197-213: D Woulfe, et al. Signal transduction during the initiation, extension, and perpetuation of platelet plug formation) In platelets, the G-protein coupled receptor $P2Y_{12}$ (previously also known as the platelet P_{2T}, $P2T_{ac}$, or $P2Y_{cyc}$ receptor) signals via Gi, resulting in a lowering of intra-cellular cAMP and full aggregation (Nature 2001; 409: 202-207 G Hollopeter, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs.). Released ADP from dense-granules will positively feedback on the P2Y12 receptor to allow full aggregation.

Clinical evidence for the key-role of the ADP-$P2Y_{12}$ feedback mechanism is provided by the clinical use of clopidogrel, an thienopyridine prodrug which active metabolite selectively and irreversibly binds to the $P2Y_{12}$ receptor, that has shown in several clinical trials to be effective in reducing the risk for cardiovascular events in patients at risk (Lancet 1996; 348: 1329-39: CAPRIE Steering committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE); N Engl J Med 2001; 345 (7): 494-502): The Clopidogrel in Unstable Angina to prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.). In these studies, the clinical benefit with a reduced bleeding risk as compared to thienopyridines (Sem Thromb Haemostas 2005; 31 (2): 195-204 JJJ van Giezen & RG Humphries. Preclinical and clinical studies with selective reversible direct $P2Y_{12}$ antagonists.

Accordingly it is an object of the present invention to provide potent, reversible and selective $P2Y_{12}$-antagonists as anti-trombotic agents.

Summary of the invention

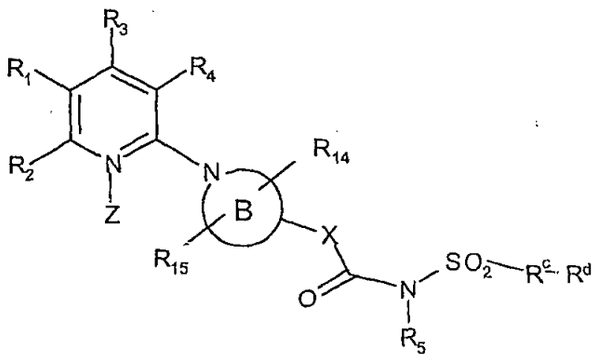
We have now surprisingly found that certain pyridine compounds of Formula (I) or a pharmaceutically acceptable salt thereof are reversible and selective $P2Y_{12}$ antagonists, hereinafter referred to as the compounds of the invention. The compounds of the invention unexpectedly exhibit beneficial properties that render them particularly suitable for use in the treatment of diseases/conditions as described below (See p.69-70). Examples of such beneficial properties are high potency, high selectivity, and an advantageous therapeutic window.



(I)

Detailed description of the invention

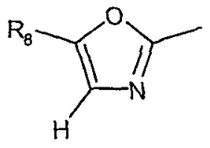
According to the present invention there is provided a novel compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

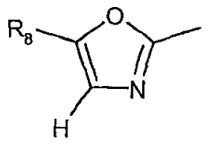
wherein

R_1 represents $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ or a group gII



(gII),

preferably R_1 represents $R_6OC(O)$, $R_{16}SC(O)$ or the group gII;



(gII).

R_2 represents H, CN, halogen (F, Cl, Br, I), NO_2, (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_1-C_{12})alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkylthioC(O), (C_1-C_{12})alkylC(S), (C_1-C_{12})alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_{12})alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_{12})alkylC(O), (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl,

heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Further, $R_1 + R_2$ together (with two carbon atoms of the pyridine ring) may form a 5-membered or 6-membered cyclic lactone;

R_3 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_1-C_{12})alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkylthioC(O), (C_1-C_{12})alkylC(S), (C_1-C_{12})alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_{12})alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_{12})alkylC(O), (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, COOH, (C_1-C_6)alkoxycarbonyl, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_4 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkylcycloalkyl, (C_1-C_{12})alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or (C_1-C_6)alkoxycarbonyl; further R_4 represents (C_1-C_{12})alkylthioC(O), (C_1-C_{12})alkylC(S), (C_1-C_{12})alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl,

arylC(O), aryl(C_1-C_{12})alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_{12})alkylC(O), (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(4)}R^{b(4)}$ in which $R^{a(4)}$ and $R^{b(4)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(4)}$ and $R^{b(4)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Z represents O or is absent;

R_5 represents H or (C_1-C_{12})alkyl;

R_6 represents (C_1-C_{12})alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 2 carbon atoms away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_{12})alkyl, aryl or heterocyclyl;

R_7 represents (C_1-C_{12})alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_7 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, aryl or heterocyclyl;

R_8 represents H, (C_1-C_{12})alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_8 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_{12})alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl, a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_{12})alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{15} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(15)}R^{b(15)}$ in which $R^{a(15)}$ and $R^{b(15)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O)), (C_1-C_{12})alkoxyC(O) or $R^{a(15)}$ and $R^{b(15)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{16} represents (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{16} represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R_{17} represents (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{17} represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl,(C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R_{18} represents (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{18} represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl,(C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R^c represents an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group, (C_1-C_4)oxoalkylene group, (C_1-C_4)alkyleneoxy or oxy-(C_1-C_4)alkylene group, wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; Further R^c represents imino (-NH-), N-substituted imino (-NR_{19}-), (C_1-C_4)alkyleneimino or N-substituted (C_1-C_4)alkyleneimino (-N(R_{19})-((C_1-C_4)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; preferably R^c represents imino or (C_1-C_4)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group or (C_1-C_4)oxoalkylene group with any substituents according to above;

R_{19} represents H or (C_1-C_4)alkyl;

R^d represents (C_3-C_8)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_{12})alkyl, (C_1-C_{12})alkoxyC(O), (C_1-C_{12})alkoxy, halogen substituted (C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(Rd)}R^{b(Rd)}$ in which $R^{a(Rd)}$ and $R^{b(Rd)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(Rd)}$ and $R^{b(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene (-CH_2-NH-) wherein the carbon is connected to the B-ring/ring system, methyleneimino (-NH-CH_2-) wherein the nitrogen is connected to the B-ring/ring system and any carbon and/or nitrogen in these groups may optionally be substitued with (C_1-C_6) alkyl; further X may represent a group (-CH_2-)n wherein n= 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or (C_1-C_6)alkyl.;

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions. The substituents R_{14} and R_{15} are connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by these connections).

Preferred values of each variable group are as follows. Such values may be used where appropriate with any of the values, definitions, claims, aspects or embodiments defined hereinbefore or hereinafter. In particular, each may be used as an individual limitation on the broadest definition of formula (I).

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

It will be understood that when formula I compounds contain a chiral centre, the compounds of the invention may exist in, and be isolated in, optically active or racemic form. The invention includes any optically active or racemic form of a compound of formula I which act as $P2Y_{12}$ receptor antagonists. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by, resolution of a racemic mixture, by chiral chromatography, synthesis from optically active starting materials or by asymmetric synthesis.

It will also be understood that the compounds of the formula I may exhibit the phenomenon of tautomerism, the present invention includes any tautomeric form of a compound of formula I which is a $P2Y_{12}$ receptor antagonist.

It will also be understood that in so far as compounds of the present invention exist as solvates, and in particular hydrates, these are included as part of the present invention.

It is also to be understood that generic terms such as "alkyl" include both the straight chain and branched chain groups such as butyl and tert-butyl. However, when a specific term such as "butyl" is used, it is specific for the straight chain or "normal" butyl group, branched chain isomers such as "t-butyl" being referred to specifically when intended.

In one embodiment alkyl is unsubstituted or substituted by one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, $(C_1\text{-}C_{12})$alkyl, $(C_1\text{-}C_{12})$alkoxyC(O), $(C_1\text{-}C_{12})$alkoxy, halogen substituted $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, heterocyclyl, $(C_1\text{-}C_{12})$alkylsulfinyl, $(C_1\text{-}C_{12})$alkylsulfonyl, $(C_1\text{-}C_{12})$alkylthio, $(C_3\text{-}C_6)$cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl$(C_1\text{-}C_{12})$alkylthio, aryl$(C_1\text{-}C_{12})$alkylsulfinyl, aryl$(C_1\text{-}C_{12})$alkylsulfonyl, heterocyclyl$(C_1\text{-}C_{12})$alkylthio, heterocyclyl$(C_1\text{-}C_{12})$alkylsulfinyl, heterocyclyl$(C_1\text{-}C_{12})$alkylsulfonyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_{12})$alkylthio, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_{12})$alkylsulfinyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_{12})$alkylsulfonyl or a group of formula NR^aR^b in which R^a and R^b independently represent H, $(C_1\text{-}C_{12})$alkyl, $(C_1\text{-}$

C_{12})alkylC(O) or R^a and R^b together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine.

The term "alkyl" includes both linear or branched chain groups, optionally substituted by one or more halogens (F, Cl, Br, I) or mixed halogen atoms.

One embodiment of alkyl when substituted by one or more halogen atoms (F, Cl, Br, I) is, for example, alkyl substituted by one or more fluorine atoms. Another embodiment of halogen substituted alkyl includes perfluoroalkyl groups such as trifluoromethyl.

The term "cycloalkyl" generally denotes a substituted or unsubstituted (C_3-C_6), unless other chain length specified, cyclic hydrocarbon.

In one embodiment cycloalkyl is substituted by one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_{12})alkyl, (C_1-C_{12})alkoxyC(O), (C_1-C_{12})alkoxy, halogen substituted (C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula NR^aR^b in which R^a and R^b independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or R^a and R^b together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine.

The term "alkoxy" includes both linear or branched chain groups, optionally substituted by one or more halogens (F, Cl, Br, I) or mixed halogen atoms.

The term aryl denotes a substituted or unsubstituted (C_6-C_{14}) aromatic hydrocarbon and includes, but is not limited to, phenyl, naphthyl, tetrahydronaphtyl, indenyl, indanyl, antracenyl, fenantrenyl, and fluorenyl.

In one embodiment aryl is substituted by one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_{12})alkyl, (C_1-C_{12})alkoxyC(O), (C_1-C_{12})alkoxy, halogen substituted (C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula NR^aR^b in which R^a and R^b independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or R^a and R^b together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine.

The term "heterocyclyl" denotes a substituted or unsubstituted, 4- to 10- membered monocyclic or multicyclic ring system in which one or more of the atoms in the ring or rings is an element other than carbon, for example nitrogen, oxygen or sulfur, especially 4-, 5- or 6-membered aromatic or aliphatic hetorocyclic groups, and includes, but is not limited to azetidine, furan, thiophene, pyrrole, pyrroline, pyrrolidine, dioxolane, oxathiolane, oxazolane, oxazole, thiazole, imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, isothiazole, oxadiazole, furazan, triazole, thiadiazole, pyran, pyridine as well as pyridine-N-oxide, piperidine, dioxane, morpholine, dithiane, oxathiane, thiomorpholine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, thiadiazine, dithiazine, azaindole, azaindoline, indole, indoline, naphthyridine, benzoxadiazole, dihydrobenzodioxin, benzothiophene, benzothiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, 3-benzisoxazole, 1,2-benzisoxazole, dihydropyrazole groups, and shall be understood to include all isomers of the above identified groups. For the above groups, e.g. azetidinyl, the term "azetidinyl" as well as "azetidinylene", etc., shall be understood to include all possible regio isomers. It is further to be understood that the term heterocyclyl may be embodified by one selection among the given possible embodiments for a variable and embodified by another (or the same) selection for another variable, eg. R_4 when selected as heterocyclyl may be a furan, when R^d (also when selected as heterocyclyl) may be a pyrrole.

In one embodiment heterocyclyl is substituted by one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_{12})alkyl, (C_1-C_{12})alkoxyC(O), (C_1-C_{12})alkoxy, halogen substituted (C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, aryl,

heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula NR^aR^b in which R^a and R^b independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or R^a and R^b together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine.

In another embodiment of the invention the heterocyclyl group comprises an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, and an aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur which is fused to a benzene ring;

In an alternative embodiment of the invention the heterocyclyl group is a non-aromatic 5-membered or 6-membered heterocyclic ring containing one, two or three heteroatoms selected from nitrogen, oxygen and sulphur, fused to a benzene ring.

In a further embodiment of the invention the heterocyclyl group is a group chosen among furyl, pyrrolyl, thienyl, pyridyl, N-oxido-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, oxazolyl, isooxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, benzfuranyl, quinolyl, isoquinolyl, benzimidazolyl, indolyl, benzdihydrofuranyl, benzodioxolyl (such as 1,3-benzodioxolyl), benzoxadiazole, dihydrobenzodioxin, benzothiophene, benzothiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, dihydropyrazole and benzdioxanyl (such as 1,4-benzdioxanyl). More particular values include, for example, furyl, pyrrolyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, benzoxadiazole, dihydrobenzodioxin, benzothiophene, benzothiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, 1,2-benzisoxazole, dihydropyrazole and benzdioxanyl (such as 1,4-benzdioxanyl).

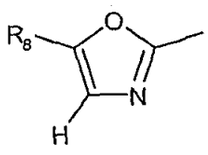
In an even further embodiment of the invention the heterocyclyl group is a group chosen among furyl, pyrrolyl, thienyl, pyridyl, N-oxido-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl,

benzoxadiazole, dihydrobenzodioxin, benzothiophene, benzothiadiazole, imidazothiazole, 2,3-dihydrobenzofuran, isoxazole, 1,2-benzisoxazole or dihydropyrazole.

In one embodiment of the invention R_1 represents $R_6OC(O)$.

In another embodiment of the invention R_1 represents $R_{16}SC(O)$.

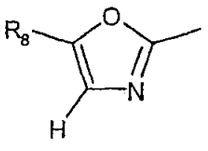
In yet another embodiment R_1 represents a group (gII),



(gII).

In a further embodiment of the invention R_1 is selected among $R_6OC(O)$ and $R_{16}SC(O)$ wherein R_6 can be methyl, ethyl, 2-hydroxyethyl, 2,2,2-trifluoroethyl, isopropyl, cyclo-propyl, iso-butyl, n-butyl, cyclo-butyl, n-propyl, tertbutyl, cyclo-pentyl, 2,2-dimethylpropyl, benzyl and 4-fluorobenzyl and wherein R_{16} is ethyl.

R_1 may also be embodified by the group gII,



(gII),

in which R_8 is selected from H, $(C_1\text{-}C_6)$alkyl, such as methyl or ethyl.

In another embodiment for the group R_8 this group can be chosen among hydrogen, methyl, ethyl, n-propyl and n-butyl.

Embodiments for R_2 include, for example, H and$(C_1\text{-}C_4)$alkyl. Other embodiments for R_2 are methyl, ethyl, iso-propyl, phenyl, methoxy, or amino unsubstituted or optionally substituted with methyl.

Embodiments for R_3 include, for example, H, methyl, methylsulfinyl, hydroxymethyl, methoxy or amino unsubstituted or optionally substituted with one or two methyl groups.

Other embodiments for R_3 include H or amino unsubstituted or optionally substituted with one or two methyl groups.

Embodiments for R_4 include H, halogen such as chloro, methyl, cyano, nitro, amino unsubstituted or optionally substituted with one or two methyl groups and further includes 4-methoxy-4-oxobutoxy, 3-carboxy-propoxy and methylcarbonyl.

In one embodiment of the invention Z is absent.

In another embodiment of the invention Z represents O.

In one embodiment R_5 represents hydrogen or methyl. In another embodiment R_5 is hydrogen.

Further embodiments for R_8 include, hydrogen, methyl and ethyl.

Further embodiments for R_{14} include, for example, hydrogen, methyl, amino, tert-butyloxycarbonyl, tert-butyloxycarbonyl-imino, 2-carboxyethyl and 3-tert-butoxy-3-oxo-propyl.

Other further embodiments for R_{14} include, for example, hydrogen, methyl, tert-butyloxycarbonyl-imino, and amino.

Embodiments for R_3 include, for example, H, methyl, methylsulfinyl, hydroxymethyl, methoxy or amino unsubstituted or optionally substituted with one or two methyl groups.

Other embodiments for R_3 include H or amino unsubstituted or optionally substituted with one or two methyl groups.

Embodiments for R_4 include H, halogen such as chloro, methyl, cyano, nitro, amino unsubstituted or optionally substituted with one or two methyl groups and further includes 4-methoxy-4-oxobutoxy, 3-carboxy-propoxy and methylcarbonyl.

In one embodiment of the invention Z is absent.

In another embodiment of the invention Z represents O.

In one embodiment R_5 represents hydrogen or methyl. In another embodiment R_5 is hydrogen.

Further embodiments for R_8 include, hydrogen, methyl and ethyl.

Further embodiments for R_{14} include, for example, hydrogen, methyl, amino, tert-butyloxycarbonyl, tert-butyloxycarbonyl-imino, 2-carboxyethyl and 3-tert-butoxy-3-oxo-propyl.

Other further embodiments for R_{14} include, for example, hydrogen, methyl, tert-butyloxycarbonyl-imino, and amino.

In one embodiment of the invention R_{15} represents H.

Further embodiments for R^d includes aryl or heterocyclyl, more particularly, aryl or aromatic heterocyclyl.

Another embodiment for R^d include, aryl such as phenyl and aromatic heterocyclyl such as thienyl.

Other embodiments of R^d include phenyl which optionally may be substituted.

In a special embodiment R^d represents aryl, heterocyclyl or (C_3-C_6)cycloalkyl, and anyone of these groups are optionally substituted with one or more halogen (F, Cl, Br, I) atoms or mixed halogen atoms, and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_{12})alkyl, (C_1-C_{12})alkoxyC(O), (C_1-C_{12})alkoxy, halogen substituted (C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(Rd)}R^{b(Rd)}$ in which $R^{a(Rd)}$ and $R^{b(Rd)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(Rd)}$ and $R^{b(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Even further embodiments for R^d include phenyl optionally substituted at the 2,3,4 or 5-positions as well as any combination thereof. Example of substituents are cyano, tetrazol-5-yl, methoxy, trifluoromethoxy, methyl, trifluoromethyl, fluoro, chloro, bromo, methylsulfonyl, nitro, 3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl. Two adjacent positions (e.g. 2,3) may also be connected to form a ring. Example of such a substituent is 2-naphtyl. Further more specific values for heteroaryls are 2-chloro-5-thienyl, 3-bromo-5-chloro-2-thienyl, 2,1,3-benzoxadiazol-4-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 5-chloro-3-methyl-1-benzothien-2-yl, 2,1,3-benzothiadiazol-4-yl, 2,5-dimethyl-3-furyl, 6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, 5-chloro-3-thienyl, 5-isoxazol-5-yl-2-thienyl, 5-isoxazol-3-yl-2-thienyl, 4-bromo-5-chloro-2-thienyl, 5-bromo-6-chloropyridin-3-yl, 5-bromo-2-thienyl, 5-pyridin-2-yl-2-thienyl, 2,5-dichloro-3-thienyl, 4,5-

In a special embodiment R^d represents aryl, heterocyclyl or (C_3-C_6)cycloalkyl, and anyone of these groups are optionally substituted with one or more halogen (F, Cl, Br, I) atoms or mixed halogen atoms, and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_{12})alkyl, (C_1-C_{12})alkoxyC(O), (C_1-C_{12})alkoxy, halogen substituted (C_1-C_{12})alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(Rd)}R^{b(Rd)}$ in which $R^{a(Rd)}$ and $R^{b(Rd)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(Rd)}$ and $R^{b(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Even further embodiments for R^d include phenyl optionally substituted at the 2,3,4 or 5-positions as well as any combination thereof. Example of substituents are cyano, tetrazol-5-yl, methoxy, trifluoromethoxy, methyl, trifluoromethyl, fluoro, chloro, bromo, methylsulfonyl, nitro, 3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-1-yl. Two adjacent positions (e.g. 2,3) may also be connected to form a ring. Example of such a substituent is 2-naphtyl. Further more specific values for heteroaryls are 2-chloro-5-thienyl, 3-bromo-5-chloro-2-thienyl, 2,1,3-benzoxadiazol-4-yl, 2,4-dimethyl-1,3-thiazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 5-chloro-3-methyl-1-benzothien-2-yl, 2,1,3-benzothiadiazol-4-yl, 2,5-dimethyl-3-furyl, 6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, 5-chloro-3-thienyl, 5-isoxazol-5-yl-2-thienyl, 5-isoxazol-3-yl-2-thienyl, 4-bromo-5-chloro-2-thienyl, 5-bromo-6-chloropyridin-3-yl, 5-bromo-2-thienyl, 5-pyridin-2-yl-2-thienyl, 2,5-dichloro-3-thienyl, 4,5-dichloro-2-thienyl,benzothien-3-yl, 2,5-dimethyl-3-thienyl, 3-thienyl,2-thienyl, 5-methylisoxazol-4-yl, pyridin-3-yl, [1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-2-thienyl, 5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl, 4-[(4-chlorophenyl)sulfonyl]-3-methyl-2-thienyl, 5-(methoxycarbonyl)-2-furyl and 4-(methoxycarbonyl)-5-methyl-2-furyl.

In one embodiment of the invention R^c represents an unsubstituted or monosubstituted or disubstituted (C_1-C_4)alkylene group wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl,

heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and R^d represents aryl, i.e R^c R^d represents an aryl-(C_1-C_4)alkylene group with any substituents according to above.

In a preferred embodiment of the invention R^c represents an unsubstituted or monosubstituted or disubstituted (C_1-C_3)alkylene group wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine , and R^d represents aryl, i.e R^c R^d represents an aryl-(C_1-C_3)alkylene group with any substituents according to above.

In a further embodiment of the invention R^c represents an unsubstituted or monosubstituted or disubstituted (C_1-C_4)alkylene group wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and R^d represents heterocyclyl, i e. R^c R^d represents a heterocyclyl-(C_1-C_4)alkylene group with any substituents according to above.

In a further preferred embodiment of the invention R^c represents an unsubstituted or monosubstituted or disubstituted (C_1-C_3)alkylene group wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine,

azetidine or aziridine, and R^d represents heterocyclyl, i e. R^c R^d represents a heterocyclyl-(C_1-C_3)alkylene group with any substituents according to above.

In a particular embodiment of the invention R^c represents a C_1-alkylene group wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxy, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine, and R^d represents aryl, i.e R^c R^d represents an aryl-C_1-alkylene group with any substituents according to above.

In one embodiment of the invention R_{19} represents hydrogen.
In another embodiment of the invention R_{19} represents methyl.

In a most particular embodiment of the invention R^c R^d represents a benzyl group, or a benzyl group which is substituted according to what is described in connection to substitution of the aryl group.

In one embodiment of the invention X represents a single bond.
In another embodiment of the invention X represents imino (-NH-) or methylene (-CH_2-). In yet another embodiment X represents imino (-NH-) . In a further embodiment X represents methylene (-CH_2-).

Suitable values for the B ring/ring system include, for example, diazepanylene, piperazinylene, piperidinylene, pyrrolidinylene and azetidinylene, wherein anyone of them may be presents in any of their isomeric forms (e.g. piperazin –tetrahydropyridazin-tetrahydropyrimidin).

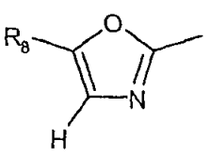
Embodiments for the B ring/ring system include, for example, diazepanylene, piperazinylene, piperidinylene, pyrrolidinylene and azetidinylene. Further embodiments include these groups which are substituted with R_{14} having a (C_1-C_6)alkyl group, wherein the (C_1-C_6)alkyl group optionally is substituted with OH, COOH or $COOR^e$ group(s), e.g. a 2-

carboxyethyl group, and wherein R^e represents H, aryl, cycloalkyl, heterocyclyl or (C_1-C_{12})alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) or mixed halogen atoms, OH, aryl, cycloalkyl and heterocyclyl.

In an alternative to the embodiment for the B ring/ring system above, the embodiment include, for example, diazepanylene, piperazinylene, piperidinylene, pyrrolidinylene or azetidinylene groups which are substituted with R_{14} having a (C_1-C_6)alkyl group, wherein the (C_1-C_6)alkyl group optionally is substituted with OH, COOH or $COOR^e$ group(s), e.g. a 2-carboxyethyl group, and wherein R^e represents H, aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) or mixed halogen atoms, OH, aryl, cycloalkyl and heterocyclyl.

A 2nd embodiment of formula I is defined by;

R_1 represents $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ or a group gII,



(gII);

R_2 represents H, CN, NO_2, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_1-C_6)alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Further, $R_1 + R_2$ together (with two carbons from the pyridine ring) may form a 5-membered or 6-membered cyclic lactone;

R_3 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_3 represents (C_1-C_6)alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, COOH, (C_1-C_6)alkoxycarbonyl, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_4 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or (C_1-C_3)alkoxycarbonyl; further R_4 represents (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(4)}R^{b(4)}$ in which $R^{a(4)}$ and $R^{b(4)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(4)}$ and $R^{b(4)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Z represents O or is absent;

R_5 represents H or (C_1-C_6)alkyl;

R_6 represents (C_1-C_6)alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 1 carbon atom away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_6)alkyl, aryl or heterocyclyl;

R_7 represents (C_1-C_6)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_7 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, aryl or heterocyclyl;

R_8 represents H, (C_1-C_6)alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_8 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, $(C_3-$

C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{15} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl,(C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl , heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)lkylsulfonyl or a group of formula $NR^{a(15)}R^{b(15)}$ in which $R^{a(15)}$ and $R^{b(15)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(15)}$ and $R^{b(15)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{16} represents (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{16} represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, or heterocyclyl;

R_{17} represents (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{17} represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R_{18} represents (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{18} represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R^c represents an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group, (C_1-C_4)oxoalkylene group, (C_1-C_4)alkyleneoxy or oxy-(C_1-C_4)alkylene group, wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; Further R^c represents imino (-NH-), N-substituted imino (-NR_{19}-), (C_1-C_4)alkyleneimino or N-substituted (C_1-C_4)alkyleneimino (-N(R_{19})-((C_1-C_4)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; preferably R^c represents imino or (C_1-C_4)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group or (C_1-C_4)oxoalkylene group with any substituents according to above;

R_{19} represents H or (C_1-C_4)alkyl;

R^d represents (C_3-C_8)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxyC(O), (C_1-C_6)alkoxy, halogen substituted (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(Rd)}R^{b(Rd)}$ in which $R^{a(Rd)}$ and $R^{b(Rd)}$ independently

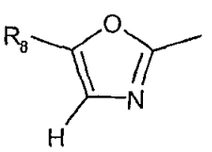
represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(Rd)}$ and $R^{b(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene (-CH_2-NH-) wherein the carbon is connected to the B-ring/ringsystem, methyleneimino (-NH-CH_2-) wherein the nitrogen is connected to the B-ring/ringsystem and any carbon and/or nitrogen in these groups may optionally be substitued with (C_1-C_6) alkyl; further X may represent a group (-CH_2-)n wherein n= 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or (C_1-C_6)alkyl.;

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions. The substituents R_{14} and R_{15} are connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by these connections).

A 3rd embodiment of formula I is defined by;

R_1 represents $R_6OC(O)$, $R_{16}SC(O)$, or a group gII,



(gII);

R_2 represents H, CN, NO_2, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_1-C_6)alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O) or a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_3 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_3 represents (C_1-C_6)alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, COOH, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_4 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or methoxycarbonyl; further R_4 represents (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O) or a group of formula $NR^{a(4)}R^{b(4)}$ in which $R^{a(4)}$ and $R^{b(4)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(4)}$ and $R^{b(4)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Z represents O or is absent;

R_5 represents H or (C_1-C_6)alkyl;

R_6 represents (C_1-C_6)alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 1 carbon atom away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_6)alkyl, aryl or heterocyclyl;

R_8 represents H, (C_1-C_6)alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms;

further R_8 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl,(C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl or a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{15} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl,(C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl or a group of formula $NR^{a(15)}R^{b(15)}$ in which $R^{a(15)}$ and $R^{b(15)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(15)}$ and $R^{b(15)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{16} is ethyl;

R^c represents an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group, (C_1-C_4)oxoalkylene group, (C_1-C_4)alkyleneoxy or oxy-(C_1-C_4)alkylene group, wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl,

$NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; Further R^c represents imino (-NH-), N-substituted imino (-NR_{19}-), (C_1-C_4)alkyleneimino or N-substituted (C_1-C_4)alkyleneimino (-$N(R_{19})$-((C_1-C_4)alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; preferably R^c represents imino or (C_1-C_4)alkyleneimino or an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group or (C_1-C_4)oxoalkylene group with any substituents according to above;

R_{19} represents H or (C_1-C_4)alkyl;

R^d represents (C_3-C_8)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, CN, NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halosubstituted (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl;

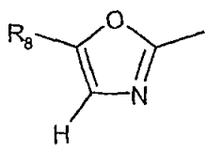
X represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene (-CH_2-NH-) wherein the carbon is connected to the B-ring/ringsystem, methyleneimino (-NH-CH_2-) wherein the nitrogen is connected to the B-ring/ringsystem and any carbon and/or nitrogen in these groups may optionally be substitued with (C_1-C_6) alkyl; further X may represent a group (-CH_2-)$_n$ wherein n= 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl or (C_1-C_6)alkyl.;

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions. The substituents R_{14} and

R_{15} are connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by these connections).

A 4rth embodiment of formula I is defined by;

R_1 represents $R_6OC(O)$, $R_{16}SC(O)$ or a group gII



(gII);

R_2 represents H or $(C_1\text{-}C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_3 represents H or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents CN, halogen (F, Cl, Br, I), further R_4 represents $(C_1\text{-}C_6)$alkylC(O), $(C_1\text{-}C_6)$alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or methoxycarbonyl;

Z represents O or is absent;

R_5 represents H;

R_6 represents $(C_1\text{-}C_{12})$alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 2 carbon atoms away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents $(C_3\text{-}C_6)$cycloalkyl or hydroxy$(C_2\text{-}C_{12})$alkyl;

R_8 represents H, (C_1-C_6)alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents or a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H;

R_{16} is ethyl;

R^c represents an unsubstituted or monosubstituted (C_1-C_4)alkylene group, (C_1-C_4)alkyleneoxy or oxy-(C_1-C_4)alkylene group, wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl; Further R^c represents imino (-NH-), N-substituted imino (-NR_{19}-);

R_{19} represents H or methyl;

R^d represents (C_3-C_8)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, CN, NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halosubstituted (C_1-C_6)alkyl;

X represents a single bond, imino (-NH-) or methylene (-CH_2-); and

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or

sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions. The substituents R_{14} and R_{15} are connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by these connections).

A 5th embodiment of formula I is defined by that;

R_1 is chosen from a group consisting of methoxycarbonyl, ethoxycarbonyl, (n-propyl)-oxycarbonyl, (iso-propyl)-oxycarbonyl, (iso-butyl)-oxycarbonyl, (tert-butyl)-oxycarbonyl, (2,2-dimethyl-propyl)-oxycarbonyl, (cyclo-propyl)-oxycarbonyl, (cyclo-butyl)-oxycarbonyl, (cyclo-pentyl)-oxycarbonyl, (2-hydroxyethyl)-oxycarbonyl), (2,2,2-trifluoroethyl)-oxycarbonyl, benzyl-oxycarbonyl, 4-fluorobenzyl-oxycarbonyl, ethylthiocarbonyl, and 5-ethyl-1,3-oxazol-2-yl;

R_2 is chosen from a group consisting of H, methyl, ethyl, isopropyl, and dimethylamino;

R_3 is chosen from a group consisting of H and amino;

R_4 is chosen from a group consisting of methoxy, chloro, cyano, (4-methoxy-4-oxobutoxy), (3-carboxy-propoxy) and methylcarbonyl;

Z represents O or is absent;

R_5 is H;

R_6 is chosen from a group consisting of methyl, ethyl, 2-hydroxyethyl, (2,2,2-trifluoroethyl), n-propyl, iso-propyl, cyclo-propyl, iso-butyl, tert-butyl, cyclo-butyl, 2,2-dimethylpropyl, cyclo-pentyl, benzyl and 4-fluorobenzyl;

R_8 is ethyl;

R_{14} is chosen from a group consisting of H, methyl, tert-butyloxycarbonyl-imino and amino;

R_{15} is H;

R_{16} is ethyl;

R^c is chosen from a group consisting of methylene ($-CH_2-$), methylmethylene ($-CH(CH3)-$), ethylene ($-CH_2CH_2-$), oxypropylene ($-OCH_2CH_2CH_2-$), imino (-NH-) and methylimino ($-N(CH_3)-$;

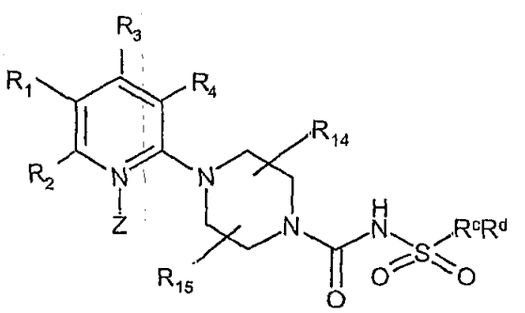
R_{19} is chosen from a group consisting of H and methyl;

R^d is chosen from a group consisting of cyclopentyl, cyclohexyl, 4-methylcyclohexyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 2-methoxycarbonyl-phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-(trifluoromethyl)phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-cyanophenyl, 4-methoxyphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 2,5-dimethylphenyl, 3,5-dimethylphenyl, 4-isopropylphenyl, 3-fluoro-4-methyl-phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, N-oxido-2-pyridyl, 6-[3-benzo[d]isoxazol-3-yl] and N-[(1,2-benzisoxazol-3-yl)];

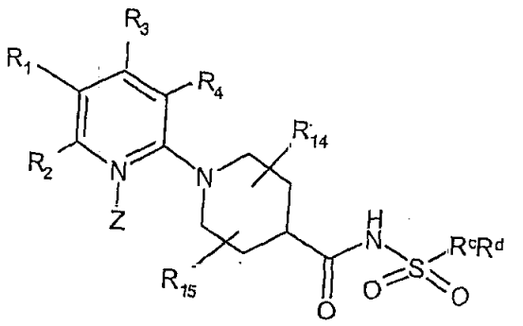
X represents a single bond, imino (-NH-) or methylene ($-CH_2-$);

B is chosen from the group consisting of 4-piperazin-1-ylene, 4-piperidin-1-ylene, 3-piperidin-1-ylene, 3-azetidin-1-ylene, and the substituents R_{14} and R_{15} are connected to the B ring/ring system, in such a way that no quarternary ammonium compounds are formed (by these connections).

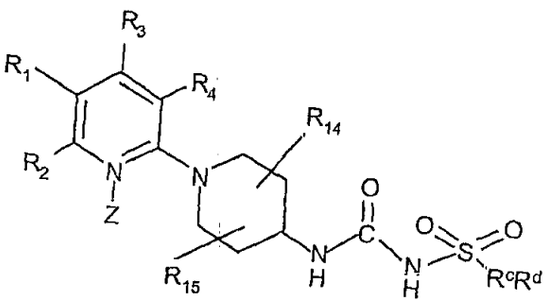
In a 6th embodiment of formula (I), formula (I) is defined as being any compound(s) of formula (Ia)-(Ii):



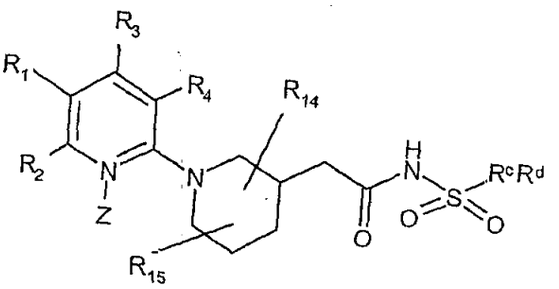
(Ia)



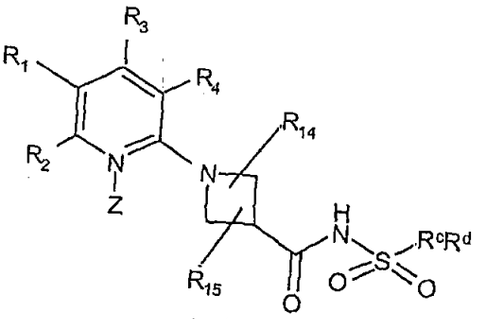
(Ib)



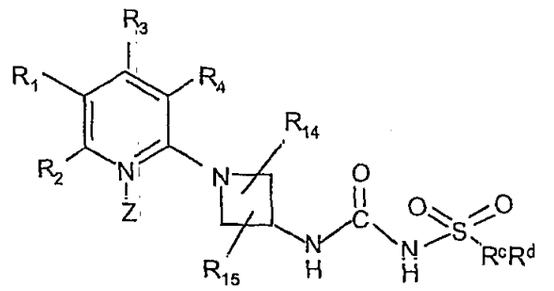
(Ic)



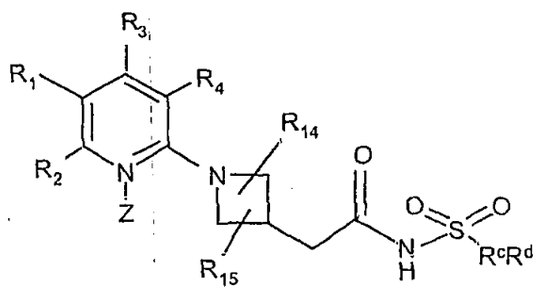
(Id)



(Ie)



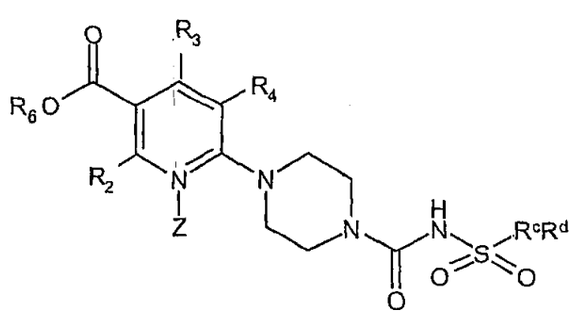
(If)



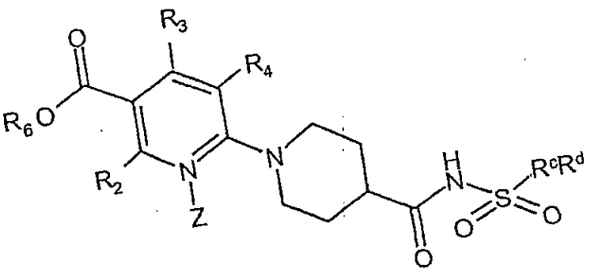
(Ig).

In the above Ia to Ig the various values of Z and R (except R_5 being H) are as defined above and include the previously mentioned embodiments.

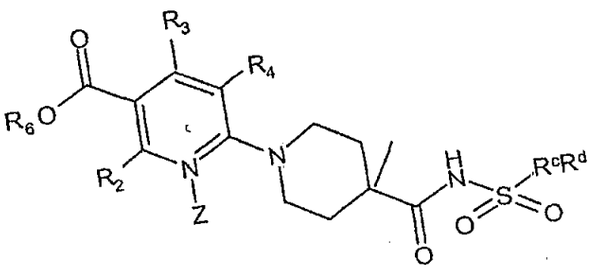
In a 7th embodiment formula (I) is defined as being any compound(s) of formula (Iaa)-(Ijj);



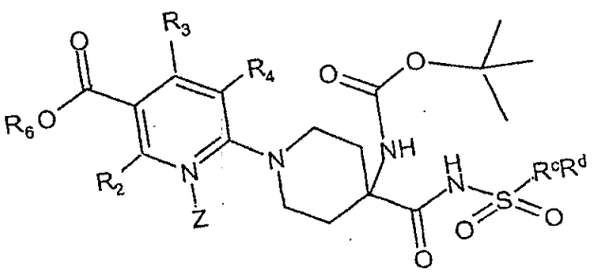
(Iaa)



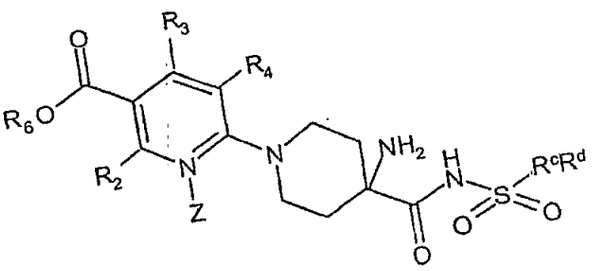
(Ibb)



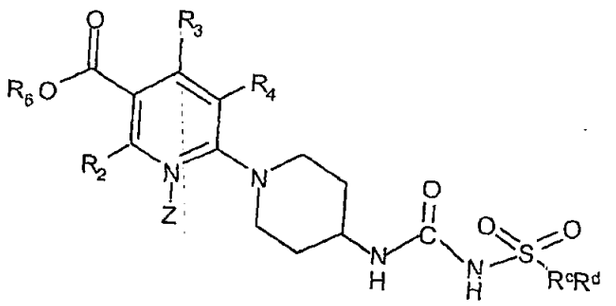
(Ibc)



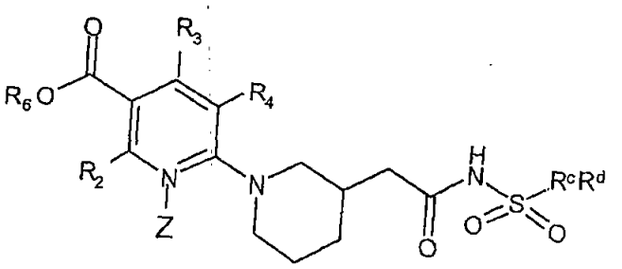
(Ibd)



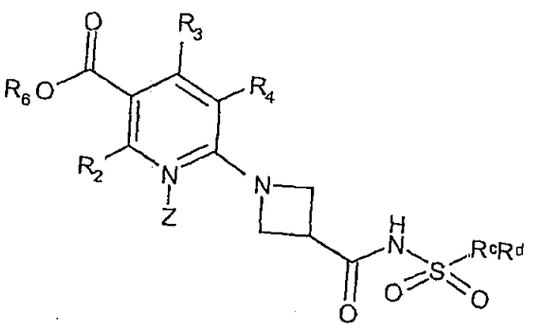
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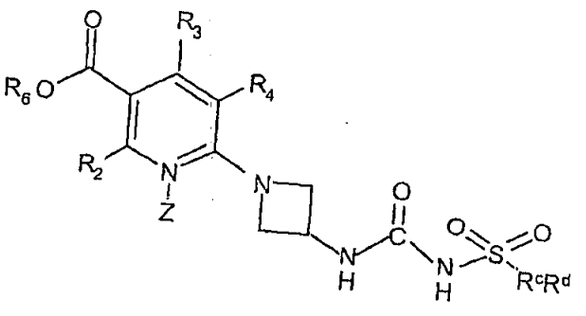
(Icc)



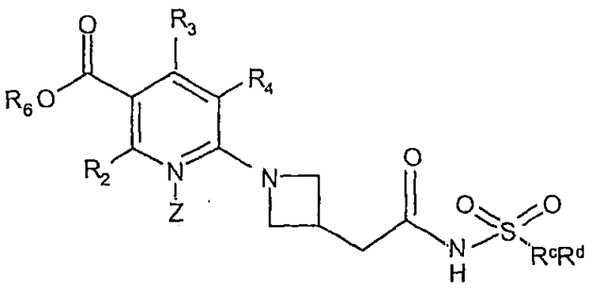
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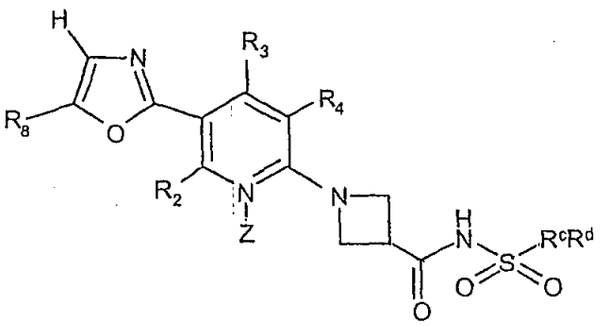
(Iee)



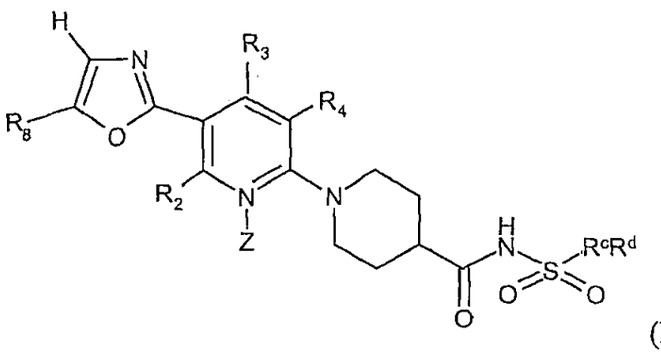
(Iff)



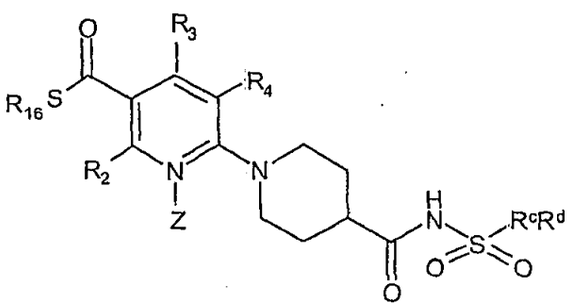
(Igg)



(Ihh)



(Iii).



(Ijj).

In the above Iaa to Ijj the various values of Z and R (except R_5, R_{14} and R_{15}, all being H) are as defined above and include the previously mentioned embodiments.

Examples of specific compounds according to the invention can be selected from;

5-Cyano-6-[3-(2-methoxycarbonyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

6-[3-({[(3-Bromobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(2-nitro-phenylmethanesulfonylaminocarbonyl)-zetidin-1-yl]-nicotinic acid ethyl ester

6-[3-(2-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

6-[3-(4-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(4-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-6-[3-(3-fluoro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(3-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

6-[3-(3-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

6-{3-[2-(3-Chloro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-5-cyano-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(4-nitro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(2-phenyl-ethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-(3-o-tolylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(3-nitro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-6-{3-[2-(4-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(2-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-6-[3-(4-fluoro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-(3-cyclopentylmethanesulfonylaminocarbonyl-azetidin-1-yl)-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-{3-[2-(2-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-[3-(3,5-dichloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-(3-cyclohexylmethanesulfonylaminocarbonyl-azetidin-1-yl)-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-{3-[2-(3-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

6-[3-(Benzo[d]isoxazol-3-ylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

1-[4-Amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]-*N*-(benzylsulfonyl)piperidine-4-carboxamide

4-Amino-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloronicotic acid ethyl ester

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid isopropyl ester

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid tert-butyl ester

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotic acid ethyl ester

6-(3-{2-[(Benzylsulfonyl)amino]-2-oxoethyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}-4-methylpiperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

N-(Benzylsulfonyl)-1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxamide

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid cyclopentyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid propyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-isopropylnicotinic acid ethyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-ethylnicotinic acid ethyl ester

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid 2,2-dimethylpropyl ester

N-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester

5-Cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinic acid ethyl ester

6-[4-({[(4-Chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

N-[(1,2-Benzisoxazol-3-ylmethyl)sulfonyl]-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

N-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]azetidine-3-carboxamide

N-[(4-Chlorobenzyl)sulfonyl]-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

ethyl 5-cyano-6-{3-[({[3-(4-methoxyphenoxy)propyl]sulfonyl}amino)carbonyl]azetidin-1-yl}-2-methylnicotinate

ethyl 4-amino-6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloronicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

2,2-dimethylpropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 6-[4-({[(3-bromobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

cyclopropyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-trifluoroethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-trifluoroethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-trifluoroethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate

cyclopropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

cyclobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

2-hydroxyethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

benzyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-isopropylnicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-ethylnicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(1-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

propyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

isobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

isopropyl 5-cyano-2-methyl-6-{4-[({[4-(trifluoromethyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

isopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

isopropyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

isopropyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

isopropyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-{4-[({[2-(methoxycarbonyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-2-methyl-6-{4-[({[2-(2-methylphenyl)ethyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

4-{[2-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

ethyl 6-(4-{[(anilinosulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-{4-[({[methyl(phenyl)amino]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

isopropyl 5-cyano-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

isopropyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-2-methyl-6-[3-({[(2-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

isopropyl 5-cyano-6-[3-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-{3-[({[2-(methoxycarbonyl)benzyl]sulfonyl}amino)carbonyl]azetidin-1-yl}-2-methylnicotinate

isopropyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate

isopropyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[3-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

methyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

methyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

S-ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylpyridine-3-carbothioate

S-ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]pyridine-3-carbothioate

S-ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylpyridine-3-carbothioate

S-ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylpyridine-3-carbothioate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-methoxy-2-methylnicotinate

ethyl 6-[4-({[(benzylsulfonyl)amino]carbonyl}amino)piperidin-1-yl]-5-cyano-2-methylnicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperazin-1-yl)-5-cyano-2-methylnicotinate

4-{[2-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid

ethyl 5-cyano-2-methyl-6-{3-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-3-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-{4-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-3-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-4-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-2-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(3,5-dimethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(2,5-dimethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

benzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-6-[3-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(2-phenylethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-2-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(2,5-dimethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloro-2-methylnicotinate

ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-(2-{[(4-fluorobenzyl)sulfonyl]amino}-2-oxoethyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(3-fluoro-4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-methylnicotinate

4-fluorobenzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(3,4-difluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-chloro-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[4-({[(3,4-difluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

cyclopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-4-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate 1-oxide

ethyl 5-acetyl-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-2-methylnicotinate

ethyl 6-{4-{[(benzylsulfonyl)amino]carbonyl}-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-cyano-2-methylnicotinate

ethyl 6-(4-amino-4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-(difluoromethyl)nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

ethyl 5-cyano-6-[3-({[(3-cyanophenyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(4-cyanophenyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

ethyl 5-cyano-6-[3-({[(2-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-(3-{[(2-naphthylsulfonyl)amino]carbonyl}azetidin-1-yl)nicotinate

ethyl 6-(3-{[(butylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(3-cyanophenyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(4-cyanophenyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-6-[4-({[(2-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

ethyl 5-cyano-2-(difluoromethyl)-6-(4-{[(2-naphthylsulfonyl)amino]carbonyl}piperidin-1-yl)nicotinate

ethyl 6-(4-{[(butylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}pyrrolidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-(2-oxo-2-{[(2-phenylethyl)sulfonyl]amino}ethyl)pyrrolidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 6-[3-(2-{[(5-chloro-2-thienyl)sulfonyl]amino}-2-oxoethyl)pyrrolidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 6-[3-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

ethyl 6-[4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

ethyl 5-cyano-2-(fluoromethyl)-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-2-(fluoromethyl)-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 5-cyano-2-(fluoromethyl)-6-{3-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

ethyl 5-cyano-2-(fluoromethyl)-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-(fluoromethyl)-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

ethyl 5-cyano-2-(fluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate;

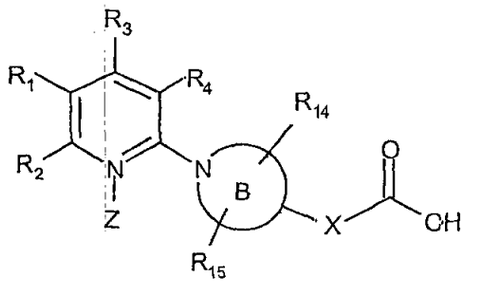
and pharmaceutically acceptable salts thereof.

Processes

The following processes together with the intermediates are provided as a further feature of the present invention.

Compounds of formula (I) may be prepared by the following processes *a1-a8;*

a1) Compounds of formula (I) in which R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z, R^c and R^d are defined as above, X is a single bond or a carbon, can be formed by reacting a compound of formula (II), in which R_1, R_2, R_3, R_4, B, Z, R_{14}, and R_{15} are defined



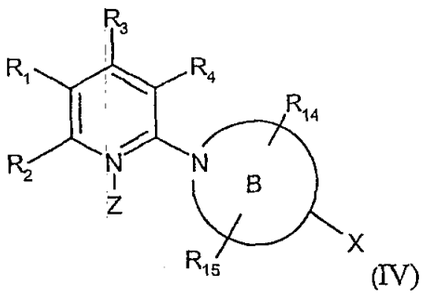
(II)

as above, X is a single bond or a carbon, with a compound of formula (III) in which R_5, R^c and R^d are defined as above.

$R_5\text{-}NHSO_2\text{-}R^c\text{-}R^d$ (III)

The reaction is generally carried out in an inert organic solvent such as dichloromethane at ambient temperature. The reaction may be carried out using standard conditions or in the presence of TBTU, EDCI or the combination of EDCI and HOBT. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

a2) Compounds of formula (I) in which R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z, R^c and R^d are defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, can be formed by reacting a compound of formula (IV), in which R_1, R_2, R_3, R_4, R_{14}, and R_{15} are defined as above and X is a nitrogen or a hydrogen, with a compound of the general

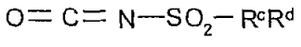


(IV)

formula (III) which is defined as above.

The reaction is generally carried out in an inert solvent such as DCM. The reaction may be carried out in the presence of CDI. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

a3) Compounds of formula (I) in which R_1, R_2, R_3, R_4, B, R_{14}, R_{15}, Z, R^c and R^d are defined as above, R_5 is a hydrogen, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, can be formed by reacting a compound of formula (IV) which is defined in *a2)* above, with a compound of formula (V)



(V)

in which R^c and R^d is as defined above.

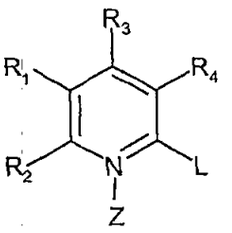
The reaction is generally carried out in an inert solvent such as THF. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

a4) Compounds of formula (I) in which R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z, R^c and R^d are defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, can be formed by reacting a compound of formula (IV) which is defined in above, with a compound of formula (VI),

$$R^dR^c\text{-}SO_2NR_5\text{-}COOCH_2CCl_3 \quad (VI)$$

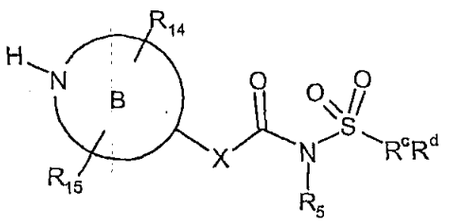
in which R_5,R^c and R^d are as defined above. The reaction is generally carried out in a solvent such as DMA. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

a5) Compounds of formula (I) may also be prepared by reacting a compound of formula (VII) in which R_1, R_2, R_3, R_4 and Z are defined as above and L is a suitable leaving group, such as chloro, bromo, iodo, fluoro, triflate or tosyl,



(VII)

with a compound of the general formula (VIII) in which B, R_5, R_{14}, R_{15}, R^c and R^d are defined as in formula (I).



(VIII)

The reaction is generally carried out in an inert solvent such as DMA. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven.

Generally, using the zwitterion of (VIII) when R_5 is H, leads to shorter reaction times than when using the corresponding salt of the B-ring amine, e.g. HCl salt.

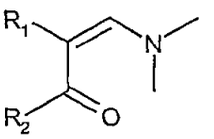
For some compounds, it is advantageous to carry out the reaction in ethanol in the presence of an organic base such as triethylamine.

a6) Compounds of formula (I) where R_1 represents $R_6OC(O)$ and R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, X, Z, R^c and R^d are defined as for formula (I), can be transesterified using standard procedures or by reacting with $R_{6'}$-O^-Li^+ reagent, to become another compound of the general formula (I) wherein R_1 becomes $R_{6'}OC(O)$.

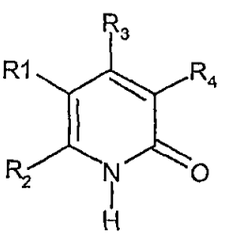
a7) A compound of formula (I) in which R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z and R^d are defined as above and R^c represents imino (-NH-) or (C_1-C_4)alkylimino in which the imino group could be substituted using standard conditions or using an alkylating agent like L-R_{19}, in which R_{19} is defined as above and L is a leaving group examplified by chloro, bromo, iodo, triflate or tosyl, to give compounds of formula (I) in which R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z and R^d are defined as above and R^c represents N-substituted imino (-NR_{19}-) or N-substituted (C_1-C_4)alkylimino (-N(R_{19})-((C_1-C_4)alkyl), optionally in the presence of a strong base such as NaH.

a8) Certain compounds of formula (I) in which R_2, R_3, R_4, B, R_{14}, R_{15}, R^c and R^d are defined as above, R_1 is $R_6OC(O)$ wherein R_6 is defined as above, X is a single bond, Z is absent and R_5 is hydrogen, are advantageously prepared by the following steps (a8:1-a8:5);

a8:1) Reacting a compound of the formula $R_1CH_2C(O)R_2$, with dimethoxy-N,N-dimethylmethaneamine to form a compound of the formula



a8:2) This compound is further reacted with a compound of the general formula $R_4CH_2C(O)NH_2$, in which R_4 is defined as for formula (I) to give a compound of the general formula



, in which R_2, R_3, R_4 are defined as

for formula (I), R_1 is $R_6OC(O)$, wherein R_6 is defined as above and Z is absent. The reaction is generally performed in an inert solvent such as ethanol. This reaction is performed in the presence of a strong base such as sodium ethoxide. The process is further advantageously performed by washing the final product with an alkaline water solution, e. g. a sodium bicarbonate solution.

a8:3) The compound from *a8:2)* is reacted with a chlorinating agent such as thionyl chloride to give a compound of formula (VII) wherein L is a chlorine. A further improvement of this reaction is to add dimethylformamide. Advantageously the reaction is performed in an inert solvent such as toluene.

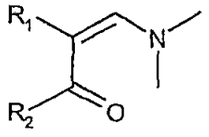
a8:4) Compounds of the general formula (VIII) in which B, R_{14}, R_{15}, R^c and R^d are defined as above, X is a single bond and R_5 is a hydrogen, are formed by reacting a compound of formula (X) with a compound of formula (III), in which the ring nitrogen is protected, for example by t-butyloxycarbonyl. The reaction is generally carried out in an inert organic solvent such as THF. The reaction is carried out using a coupling reagent such as TBTU. Optionally, the reaction is carried out in the presence of an organic base such as triethylamine or DIPEA. A further improvement of this reaction is to add LiCl. When the product contains a t-butyloxycarbonyl this group is removed using standard procedures or in the presence of formic acid. In one advantageous embodiment of the process *(a8)* the product is isolated as a zwitterion by adjusting the pH of the reaction mixture to between approximately 5-9 with ammonia dissolved in water.

a8:5) The product from *a8:3* is reacted with the product from *a8:4*, preferentially the zwitterion, to give a compound of formula (I) in which R_2, R_3, R_4, B, R_{14}, R_{15}, R^c and R^d are defined as above, R_1 is $R_6OC(O)$ wherein R_6 is defined as above, X is a single bond, Z is absent and R_5 are hydrogen. The reaction is generally carried out in an inert solvent such as ethanol at elevated temperatures. Optionally, the reaction is carried out in the presence of an organic base such as triethylamine. In one advantageous embodiment of the process *(a8)* the final product is purified and isolated by recrystallisation from ethyl acetate.

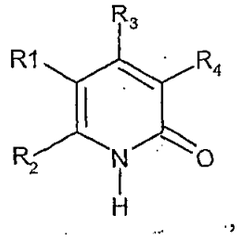
Thus, in one embodiment of the invention, an advantageous process for manufacturing a compound of formula (I) in which R_2, R_3, R_4, R_6, B, R_{14}, R_{15}, R^c and R^d are defined according

to above, R_1 is $R_6OC(O)$ wherein R_6 is defined as above, X is a single bond, Z is absent and R_5 is hydrogen exists, characterised in that the process comprises the following steps (i-vi);

i.) Reacting a compound of the formula $R_1CH_2C(O)R_2$, with dimethoxy-N,N-dimethylmethaneamine to form a compound of the formula



ii.) Reacting the compound from step i.) with a compound of the general formula $R_4CH_2C(O)NH_2$ in an inert solvent such as ethanol in the presence of a strong base such as sodium ethoxide, to give a compound of the general formula



in which R_2, R_3, R_4, are defined according to above, R_1 is $R_6OC(O)$ wherein R_6 is defined according to above, and Z is absent.

iii) The product from step ii) is first washed with an alkaline water solution, e. g. a sodium bicarbonate solution and then washed with water whereafter the washed product is collected.

iv.) The compound from step iii) is reacted with a chlorinating agent such as thionyl chloride in an inert solvent, to give a compound of formula (VII) wherein L is a chlorine.

v.) reacting a compound of formula (X) with a compound of formula (III), in which B, R_{14}, R_{15}, R^c and R^d are defined according to above, X is a single bond and R_5 is a hydrogen, while the compound of formula (III) is having the ring nitrogen protected by t-butyloxycarbonyl, in an inert organic solvent, in the presence of a coupling reagent and optionally an organic base such as triethylamine or DIPEA, to give a compound of the general formula (VIII) after standard deprotection of the t-butyloxycarbonyl.

vi) The product from step v.) is reacted with the product from step iv.) in an inert solvent, optionally in the presence of an organic base such as triethylamine, to give a compound of formula (I) in which R_2, R_3, R_4, B, R_{14}, R_{15}, R^c and R^d are defined according to above, R_1 is $R_6OC(O)$ and R_6 is defined according to above, X is a single bond, Z is absent and R_5 is hydrogen.

In a separate embodiment of the process step iv.) comprises adding dimethylformamide to the reaction mixture.

In another separate embodiment of the advantageous process the process step iv.) comprises adding dimethylformamide to the reaction mixture and the inert solvent in step iv.) is toluene.

In another separate embodiment of the advantageous process it is possible to combine one or more of the previous process embodiments with selecting the inert organic solvent in step v.) to be THF.

In a further separate embodiment of the process it is possible to combine one or more of the previous process embodiments with selecting that the coupling reagent in step v.) is TBTU.

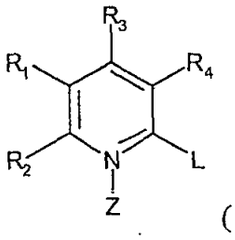
In a further separate embodiment of the advantageous process it is possible to combine one or more of the previous process embodiments with adding LiCl to the reaction mixture in step v.).

In an even further separate embodiment of the advantageous process it is possible to combine one or more of the previous process embodiments with isolating the product obtained in step v.) by adding ammonia dissolved in water.

In an even further separate embodiment of the advantageous process it is possible to combine any of the previous process embodiments with purifying and isolating the product from step vi) by recrystallisation from ethyl acetate.

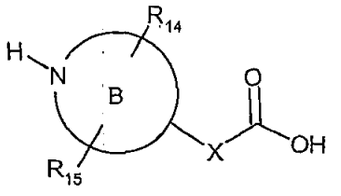
The intermediates referred to above may be prepared by, for example, the methods/processes outlined below.

b) The compounds of formula (II) in which R_1, R_2, R_3, R_4, B, Z, R_{14}, and R_{15} are defined as above, X is a single bond or a carbon, may be prepared by reacting a compound of formula (IX)



(IX)

, in which R_1, R_2, R_3, R_4 and Z are defined as for formula (I) above and L is a suitable leaving group (such as fluoro, chloro, bromo, iodo, triflate or tosyl), with a compound of the general formula (X),

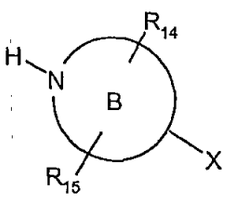


(X)

in which B, R_{14}, R_{15} are defined as above and X is a single bond or a carbon.

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven. The reaction can be carried out in an inert solvent such as ethanol, DMA or a mixture of solvents such as ethanol-water. Optionally the reaction may be carried out in the prescence of an organic base base such as TEA or DIPEA.

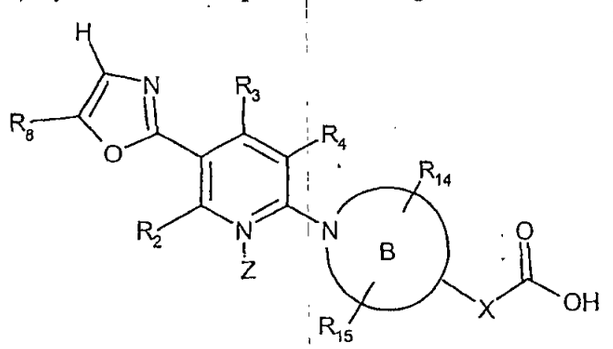
c) Compounds of formula (IV) which are defined as above may be prepared by reacting the corresponding compound of formula (IX) which is defined above, with a compound of formula (XI) in which B, R_{14}, R_{15} are defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring.



(XI)

The reaction is generally carried out at elevated temperatures using standard equipment or in a single-node microwave oven. The reaction can be carried out in an inert solvent such as ethanol, DMA or a mixture of solvents such as ethanol-water. Optionally the reaction may be carried out in the prescence of an organic base base such as TEA or DIPEA.

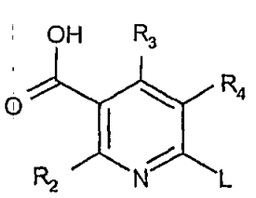
d) Synthesis of compounds of the general formula (XXX),



(XXX)

in which R_2, R_3, R_4, B, R_8, R_{14} and R_{15} are defined as above and X is a carbon or a single bond comprises the below steps. (d1-d5)

d1) Reacting the corresponding compounds of the general formula (X) which is defined as above with a compound of the general formula (XXI)

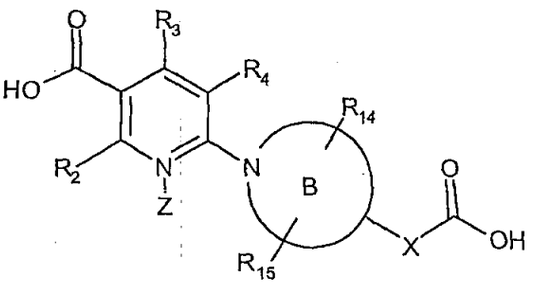


(XXI)

in which R_2, R_3 and R_4 are defined as for formula I, and L is a suitable leaving group, such as chloro, bromo, iodo, triflate or tosyl, to give a compound of formula (XXII).

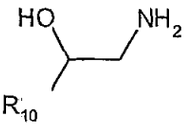
The reactions are carried out at elevated temperatures using standard equipment or a single-node microwave oven. Optionally the reaction may be carried out in the prescence of an organic base such as TEA or DIPEA.

d2) The compounds of formula (XXII) can then be reacted



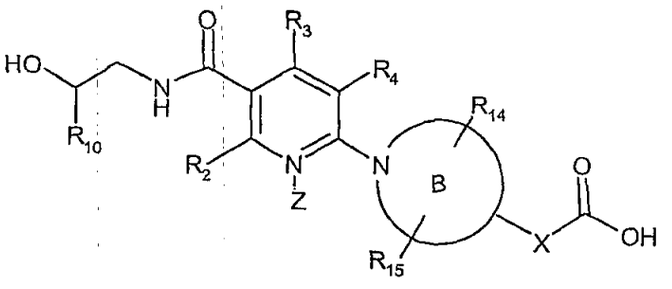
(XXII)

with a compound of the general formula (XXIII),



(XXIII)

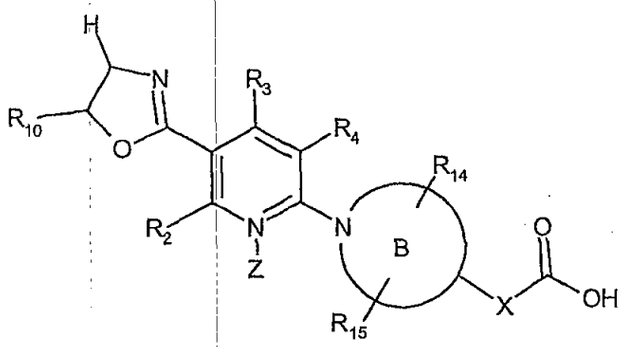
in which R_{10} is defined as above, to give compounds of the general formula (XXIV). The reactions are carried out using standard conditions or in the prescence of EDCI or the combination of EDCI and HOBT. Optionally the reaction may be carried out in the prescence of an organic base such as TEA or DIPEA.



(XXIV)

d3) This compound (XXIV) can then be transformed to a compound of the general formula (XX)

d4) The preparation of compounds with the general formula (XX),



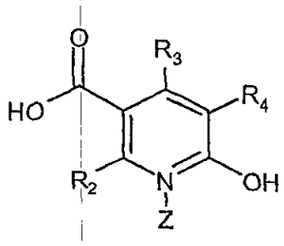
(XX)

in which R_2, R_3, R_4, B, R_{10}, R_{14} and R_{15} are defined as above and X is a carbon or a single bond using known methods or a known reagent such as methanesulfonyl chloride. Optionally the reaction may be carried out in the prescence of an organic base such as TEA.

d5) can be made by oxidising the corresponding compound of the general formula (XX) wherein R_{10} is the same substituent as to R_8, using a known oxidation reagent such as DDQ.

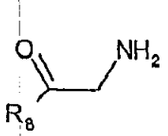
e) The preparation of compounds of the general formula (XXX) also comprises the steps (*e1-e4*) below;

e1) Reacting a compound the general formula (XXXI),



(XXXI)

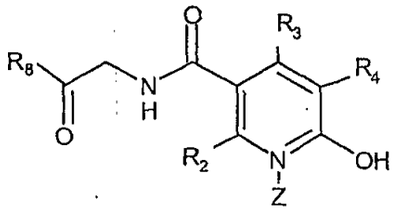
in which R_2, R_3 and R_4 are defined as for compound (I) above, with a compound of the general formula (XXXII), in which R_8 is defined as above,



(XXXII)

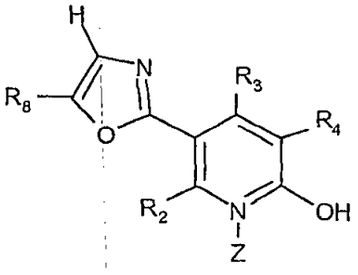
using standard conditions or in the prescence of EDCI or the combination of EDCI and HOBT. Optionally the reaction may be carried out in the prescence of an organic base such as TEA. This reaction gives a compound of the general formula (XXXIII).

e2) The compound of the general formula (XXXIII) obtained



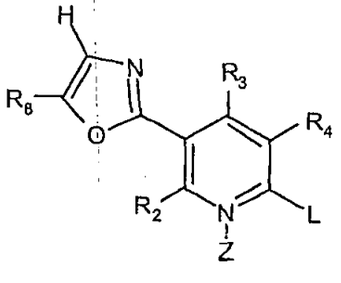
(XXXIII)

can then be transformed to a compound of the general formula (XXXIV), in which R_2, R_3, R_4 and R_8 are defined as above, using known techniques or using a known reagent such as $POCl_3$.



(XXXIV)

e3) A compound of the general formula (XXXIV) can then be transformed to a compound of the general formula (XXXV),

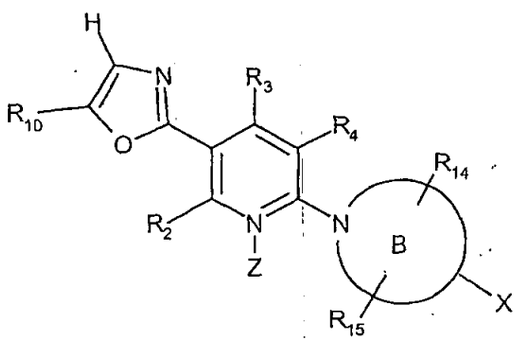


(XXXV)

in which R_2, R_3, R_4, R_8 are defined as above and L is a sufficent leaving group, such as chloro, bromo, iodo, triflate or tosyl, using a known techniques or a reagent such as oxalyl chloride or thionyl chloride.

e4) The compound of formula (XXXV) can then be reacted with a compound of the general formula (X), which is defined as above, to give a compound of the general formula (XXX), defined as above. The reactions are carried out at elevated temperatures using standard equipment or a single-node microwave oven. Optionally the reactions may be carried out in the prescence of an organic base such as TEA or DIPEA.

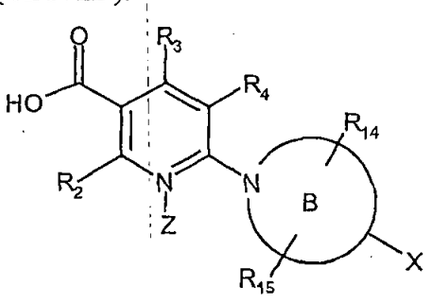
*f)*Preparation of Compounds of the general formula (XXXVI),



(XXXVI)

in which R_2, R_3, R_4, B, R_{10}, R_{14} and R_{15} are defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, comprises the below steps. *(f1-f4)*

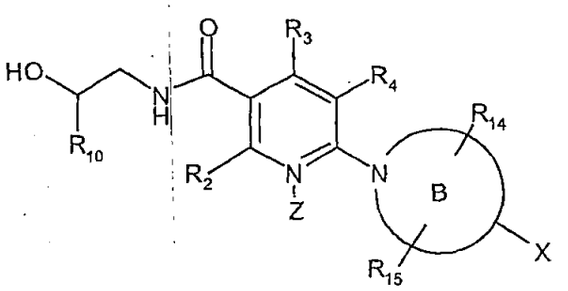
f1) Reacting a compound of the general formula (XI) which is defined as above with a compound of the general formula (XXI) which is defined as above, to give a compound of the general formula (XXVIII).



(XXVIII)

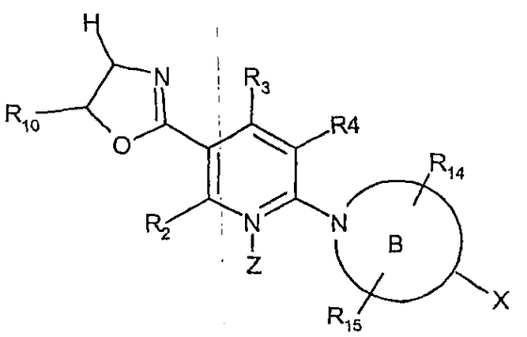
The reactions are carried out at elevated temperatures using standard equipment or a single-node microwave oven. Optionally the reaction may be carried out in the prescence of an organic base such as TEA or DIPEA.

f2) The compound of formula (XXVIII) can be reacted with a compound of formula (XXIII), which is defined as above, to give compounds of the general formula (XXIX). The reactions are carried out using standard conditions or in the prescence of EDCI or the combination of EDCI and HOBT. Optionally the reactions may be carried out in the prescence of an organic base such as TEA or DIPEA.



(XXIX)

f3 This compound can then be transformed to a compound of the general formula (XXVI) in which R_2, R_3, R_4, B, R_{10}, R_{14} and R_{15}, are defined as above,



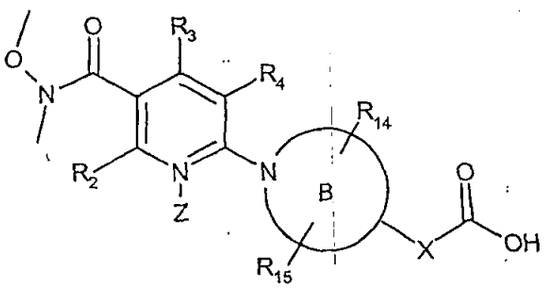
(XXVI)

X is a nitrogen or a hydrogen connected to a nitrogen which is a member of the B ring, using known methods or a sufficent reagent such as methanesulfonyl chloride. Optionally the reaction may be carried out in the prescence of an organic base such as TEA.

f4) (XXXVI) can then prepared by oxidising a compound of the general general formula (XXVI), which is defined as above. The reaction can be performed using standard conditions or a reagent like DDQ.

Compounds of the general formula (II), in which R_1 is $R_7C(O)$, R_2, R_3, R_4, B, R_{14} and R_{15} are defined as above, X is a single bond comprises the following steps *(g1-g2):*

g1) Reacting a compound of the general formula (XXII), described above, with N,O-dimethylhydroxylamine. The reaction can be performed using known reagents like CDI to give a compound of the general formula (XXXVIII).

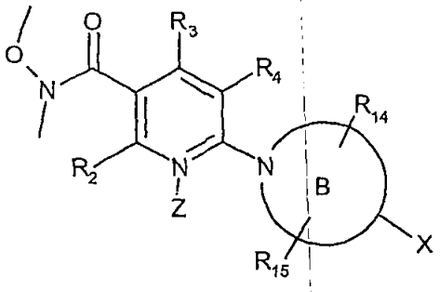


(XXXVIII)

g2) Reacting compounds of the general formula (XXXVIII), defined as above, with a reagent of the general formula R_7-MgX, in which R_7 is defined as above and X is a halogen, or a reagent of the formula R_7-M, in which M is a metal examplified by Zn and Li.

Compounds of the general formula (IV), in which R_1 is $R_7C(O)$, R_2, R_3, R_4, B, R_{14} and R_{15} are defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, comprises the following steps*(h1-h2)*.

h1) Reacting a compound of the general formula (XXVIII), defined as above, with N,O-dimethylhydroxylamine. The reaction can be performed using known reagents like CDI to give a compound of the general formula (XLI).



(XLI)

h2) A compound of the general formula (XLI), which is defined as above can be reacted with a reagent of the general formula R_7-MgX, in which R_7 is defined as above and X is a halogen, or a reagent of the formula R_7-M, in which M is a metal exemplified by Zn and Li.

Compounds of the general formula (VIII) can be formed in one of the processes *(i1-i5)*. The compounds of formula (VIII) in which R_5 is a hydrogen are advantageously isolated as a zwitterion. A ring nitrogen of compounds of formula (X) and (XI) used in the below steps may be protected by a protective group such as t-butyloxycarbonyl.

i1) Compounds of the general formula (VIII) in which B, R_5, R_{14}, R_{15}, R^c and R^d are defined as above, X is a single bond or a carbon, may be formed by reacting a compound of formula (X) with a compound of formula (III). The reaction is generally carried out in an inert organic solvent such as dichloromethane at ambient temperature. The reaction may be carried out using standard conditions or in the presence of EDCI or the combination of EDCI and HOBT. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA.

i2) Compounds of the general formula (VIII) in which B, R_5, R_{14}, R_{15}, R^c and R^d are defined as above, X is a single bond or a carbon, may also be formed by reacting a compound of formula (X) with a compound of formula (III), in which the nitrogen in the B-ring is protected, for example by t-butyloxycarbonyl. The reaction is generally carried out in an inert organic solvent such as THF. The reaction may be carried out using standard conditions or in the presence of TBTU. Optionally, the reaction may be carried out in the presence of an organic base such as triethylamine or DIPEA. Advantageously a reagent such as LiCl may be used. When the product contains a t-butyloxycarbonyl this may be removed using standard

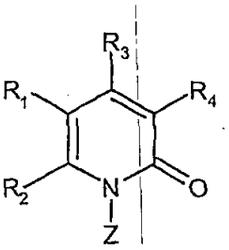
procedures or in the presence of formic acid. When R_5 is a hydrogen, compound (VIII) can be isolated as a zwitterion.

i3) Compounds of the general formula (VIII) in which R_5 is hydrogen, B, R_{14}, R_{15}, R^c and R^d are defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, can be formed by reacting a compound of formula (XI) defined as above with a compound of formula (V), defined as above. The reaction is generally carried out in an inert solvent such as THF. The reaction may also be carried out in the presence of an organic base such as triethylamine or DIPEA.

i4) Compounds of the general formula (VIII) in which B, R_5, R_{14}, R_{15}, R^c and R^d defined as above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring, can also be formed by reacting a compound of formula (XI) with a compound of formula (VI) which is defined as above. The reaction is generally carried out in a solvent such as DMA. This reaction may also be carried out in the presence of an organic base such as triethylamine or DIPEA

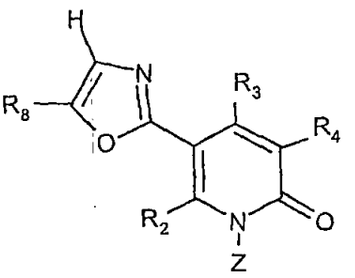
i5) A compound of formula (VIII) which is protected with t-butoxy carbonyl may be transformed into a compound without the protective group using standard procedures or a reagent such as formic acid.

(j) Compounds of the general formula (VII) which are defined as above can be formed by reacting a compound of formula (XLVI) using standard conditions or with a chlorinating reagent such as thionyl chloride or $POCl_3$. Advantageously dimethylformamide may be used. The reaction may be performed in an inert solvent. Advantageously the inert solvent is toluene.



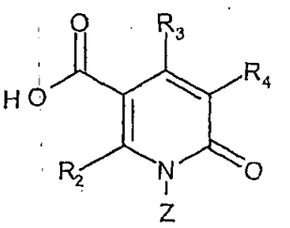
(XLVI)

The preparation of compounds of the general formula (XLVII) which is defined as above comprises the steps *(k1-k3)* below;



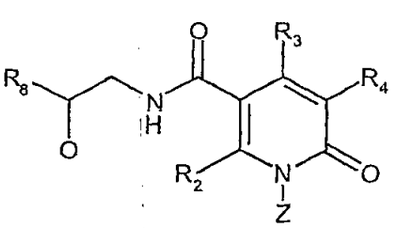
(XLVII)

k1) Reacting a compound of the general formula (XLVIII)



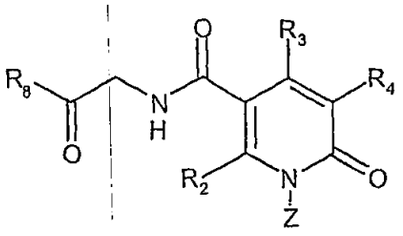
(XLVIII)

with a compound of the general formula (XXIII), which is having R_8 instead of R_{10}, otherwise defined as above, to give a compound of the formula (IL). The reaction is generally carried out in DCM at ambient temperature. The reaction may be carried out using standard conditions or in the presence of EDCI or the combination of EDCI and HOBT. Optionally the reaction may be carried out in the prescence of an organic base such as TEA or DIPEA.



(IL)

k2) The compound of formula (IL) can be transformed to a compound (L) using standard conditions or an oxidising agent such as the mixture of oxalylchloride and DMSO.



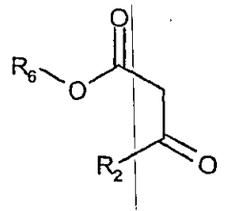
(L)

k3) The compound of formula (L) can then be tranformed into a compound of the general formula (XLVII), using standard conditions or in the presence of (Methoxycarbonylsulfamoyl)triethylammonium hydroxide (Burgess reagent). The reaction is generally performed in an inert solvent such as THF. The reaction is carried out at elevated temperatures using standard equipment or a single-node microwave oven.

Compounds of the general formula (III) can be formed by reacting the corresponding sulfonyl chloride using known methods with ammonia in an inert solvent such as methanol.

l) Preparation of compounds of the general formula (XLVIII) which is defined as above except for R_3 which is hydrogen, comprises the following steps (*l1*-*l3*);

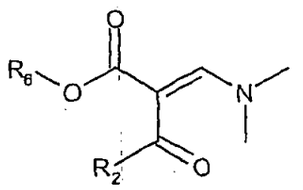
l1) Reacting a compound of the formula (LI), in which R_2 and R_6 are defined as for formula (I) with dimethoxy-N,N-dimethylmethaneamine to form a



(LI)

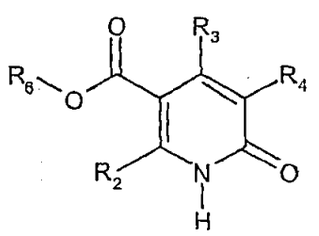
compound of formula (LII).

l2) This compound (LII) can then be reacted further with a compound of the



(LII)

general formula $R_4CH_2C(O)NH_2$, in which R_4 is defined as for formula (I) to give a compound of the general formula (LIII). The reaction is generally performed in an inert solvent such as ethanol, optionally in the presence of a strong base such as sodium ethoxide.

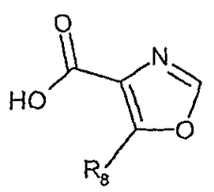


(LIII)

(l3) A compound of the general formula (LIII) can then be transformed to a compound of the general formula (XLVIII). The reaction is generally performed in a protic solvent such as water together with a co-solvent such as THF or methanol. The reaction can be performed using standard reagents or in the presence of LiOH, NaOH or KOH.

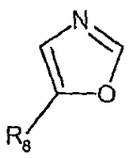
(m) The formation of a compound of the general formula (XXX), which is defined as above can be made the below synthesis;

m1) A compound of the general formula (LIV) where R_8 is defined as fo formula (I) above can be



(LIV)

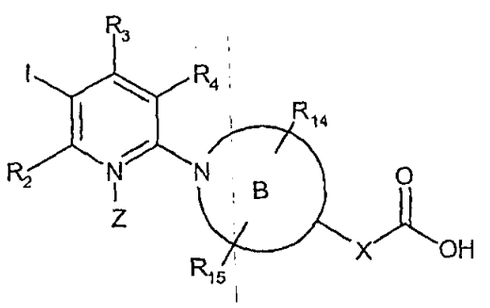
transformed in to a compound of the formula (LV)



(LV)

using standard conditions or using Cu(II)O and quinoline.

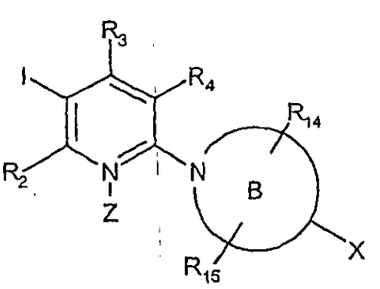
m2) The compound of the general formula (LV) can be reacted with a compound of the general formula (LVI) in



(LVI)

which R_2, R_3, R_4, B, R_{14} and R_{15} are defined as for formula (I) and X is a carbon or a single bond, to give compounds of the general formula (XXX). The reaction is generally performed in an inert solvent such as THF under inert atmosphere. The reaction can be performed using standard condtions or in the presence of AlkylLi such as BuLi, $ZnCl_2$, $Pd(Ph_3)_4$.

(n) Compounds of the general formula (XXXVI) can also be made by the step below;

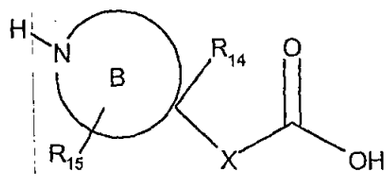


(LVII)

n1) Reacting a compound of the general formula (LV), which is defined as above, with a compound of the general formula (LVII), in which R_2, R_3, R_4, B, R_{14} and R_{15} are defined as

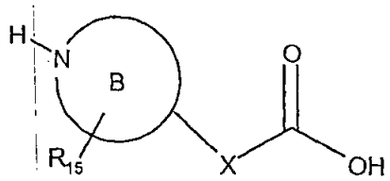
in formula (I) above, X is a nitrogen or a single bond connected to a nitrogen which is a member of the B ring.

o) The preparation of compounds of the general formula (LVIII), in which R_{14} and R_{15} are defined as for formula (I) with the exception that R_{14} is connected to the same atom as X, and X is defined as a single bond, comprises the below step;



(LVIII)

o1) Reacting the corresponding (LIX) with R_{14}-L, wherein L is a suitable leaving group, such as chloro, bromo, iodo,



(LIX)

triflate or tosyl to form compounds of the general formula (LVIII), using standard conditions or in the presence of with BuLi and diisopropylamine mixture.

The preparation of compounds of the formula (III) comprises the below processes. *(p1-p3)*

p1) A compound of the formula LR^cR^d wherein L is a suitable leaving group, such as chloro, bromo, iodo could be transformed to the corresponding compound (III) using a sequence of reactions using first SMOPS* (*Baskin and Wang. Tetrahedron Letters, 2002, 43, 8479-83. See esp. page 8480, left hand column.) followed by hydrolysis using a base like NaOMe in an inert solvent like DMSO at room temperature. Followed by treatment by NH_2OSO_3H and NaOAc to give a compound of formula (III).

p2) A compound of the formula $LSO_2R^cR^d$ wherein L is a suitable leaving group, such as chloro, bromo, iodo could be reacted with ammonium hydroxide or H_2NR_5 in an inert solvent such as DCM to give a compound of formula (III).

p3) A compound of the formula LR^cR^d wherein L is a suitable leaving group, such as chloro, bromo, iodo could be transformed to the corresponding compound (III) using a sequence of reactions first $NaSO_3$, followed by a using a reagent such as PCl_5, $POCl_3$ or $SOCl_2$, followed by ammoium hydroxide or H_2NR_5 to give a compound of formula (III).

At any stage in the synthesis of amine substituted pyridines, a chlorine subsituent in the 2, 4 or 6 position of the pyridine can be substituted with azide using known techniques. The azide can be reduced to the corresponding amine. These amines can subsequently be alkylated or acylated using known methods or with an alkylhalide or acylhalide, respectively.

Persons skilled in the art will appreciate that an acid can be transformed to the corresponding activated ester such as an acid chloride, followed by reaction with a thiol, $R_{16}SH$ to give thioesters, $R_{16}SC(O)$.

Persons skilled in the art will appreciate that an acid can be transformed to the corresponding activated ester such as an acid chloride, followed by reaction with a alcohol, R_6OH to give esters, $R_6OC(O)$.

Persons skilled in the art will appreciate that a compound of formula (III) could be alkylated at the carbon atom in the alpha position to the sulfoneamide using an alkylhalide. Preferably under basic conditions using a strong base such as sodium hydride.

Persons skilled in the art will appreciate that a nitrogen substituent at the 3 position of a pyridine could be replaced by a thioether chain, $R_{17}S$-, using known techniques or $R_{17}SSR_{17}$ and tert-Butylnitrite.

Persons skilled in the art will appreciate that a thioketone could be made from the corresponding ketone using known techniques or using Lawessons reagent.

Persons skilled in the art will appreciate that a pyridine N-oxide could be formed by from a pyridine using an oxidising agent such as Urea hydrogen peroxide or hydrogen peroxide, with or without the presence of trifluoroaceticanhydrid.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

It will be appreciated that by those skilled in the art that the processes described above and hereinafter the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include optionally substituted and/or unsaturated alkyl groups (e.g. methyl, allyl, benzyl or *tert*-butyl), trialkyl silyl or diarylalkylsilyl groups (e.g. *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for carboxylic acids include (C_1-C_6)alkyl or benzyl esters. Suitable protecting groups for amino include t-butyloxycarbonyl, benzyloxycarbonyl, 2-(trimethylsilyl)ethoxymethyl or 2-trimethylsilylethoxycarbonyl (Teoc).

The protection and deprotection of functional groups may take place before or after any reaction in the above mentioned procesess.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intemediates to

those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessery, the need for protecting groups.

Persons skilled in the art will appreciate that starting materials for any of the above processes can in some cases be commercially available.

Persons skilled in the art will appreciate that processes above could for some starting materials above be found in the general common knowledge.

The type of chemistry involved will dictate the need for protecting groups as well as sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M Wutz, Wiley-Interscince (1999).

Protected derivatives of the invention may be converted chemically to compounds of the invention using standard deprotection techniques (e.g. under alkaline or acidic conditions). The skilled person will also appreciate that certain compounds of Formula (II)-(LIX) may also be referred to as being "protected derivatives"

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventinal techniques, e.g. chromatography or crystallization. The various stereisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. HPLC techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diasteromeric derivatives by conventionals means (*e.g.* HPLC, chromatography over silica or crystallization). Stereocenters may also be introduced by asymmetric synthesis, (e.g metalloorganic reactions using chiral ligands). All stereoisomers are included within the scope of the invention.

All novel intermediates form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by

C_1-C_6-alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, tetrahydrofuran or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

Pharmacological data

Functional inhibition of the $P2Y_{12}$ receptor can be measured by in vitro assays using cell membranes from $P2Y_{12}$ transfected CHO-cells, the methodology is indicated below.

Functional inhibition of 2-Me-S-ADP induced $P2Y_{12}$ signalling: 5µg of membranes were diluted in 200 µl of 200mM NaCl, 1mM $MgCl_2$, 50mM HEPES (pH 7.4), 0.01% BSA, 30µg/ml saponin and 10µM GDP. To this was added an EC_{80} concentration of agonist (2-methyl-thio-adenosine diphosphate), the required concentration of test compound and 0.1 µCi ^{35}S-GTPγS. The reaction was allowed to proceed at 30°C for 45 min. Samples were then transferred on to GF/B filters using a cell harvester and washed with wash buffer (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). Filters were then covered with scintilant and counted for the amount of ^{35}S-GTPγS retained by the filter. Maximum activity was that determined in the presence of the agonist and minimum activity in the absence of the agonist following subtraction of the value determined for non-specific activity. The effect of compounds at various concentrations was plotted according to the equation

y = A+((B-A)/(1+((C/x)^D)))

and IC_{50} estimated where

A is the bottom plateau of the curve i.e. the final minimum y value

B is the top of the plateau of the curve i.e. the final maximum y value

C is the x value at the middle of the curve. This represents the log EC_{50} value when A + B = 100

D is the slope factor.

x is the original known x values.

Y is the original known y values.

Most of the compounds of the invention have an activity, when tested in the functional inhibition of 2-Me-S-ADPinduced $P2Y_{12}$ signalling assay described, at a concentration of around 4 μM or below.

For example the compounds described in Examples 91 and 119 gave the following test result in the functional inhibition of 2-Me-S-ADPinduced $P2Y_{12}$ signalling assay described.

	$IC_{50}(\mu M)$
Example 91	0.46
Example 119	0.25

The compounds of the invention act as $P2Y_{12}$ receptor antagonists and are therefore useful in therapy. Thus, according to a further aspect of the invention there is provided a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in therapy.

In a further aspect there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment of a platelet aggregation disorder. In another aspect of the invention there is provided the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the inhibition of the $P2Y_{12}$ receptor.

The compounds are useful in therapy, especially adjunctive therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, promoters of platelet disaggregation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-

eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process.

According to the invention there is further provided the use of a compound according to the invention in the manufacture of a medicament for the treatment of the above disorders. In particular the compounds of the invention are useful for treating myocardial infarction, thrombotic stroke, transient ischaemic attacks, peripheral vascular disease and angina, especially unstable angina. The invention also provides a method of treatment of the above disorders which comprises administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to the invention.

In a further aspect the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent, adjuvant and/or carrier.

The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided. The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres, which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved either in a readily volatile organic solvent or an aqueous solvent.

For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol , mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The invention will be further illustrated with the following non-limiting examples:

Examples

General Experimental Procedure

Mass s pectra was recorded on a Finnigan LCQ Duo ion trap mass spectrometer equipped with an electrospray interface (LC-ms) or LC-ms system consisting of a Waters ZQ using a LC-Agilent 1100 LC system.

1H NMR measurements were performed on a Varian Mercury VX 400 spectrometer, operating at a 1H frequency of 400 and Varian UNITY plus 400,500 and 600 spectrometers, operating at 1H frequencies of 400,500 and 600 respectively. Chemical shifts are given in ppm with the solvent as internal standard. Chromatography was performed using Biotage silica gel 40S, 40M, 12i or Merck silica gel 60 (0.063-0.200mm). Flashchromatography was performed using either standard glass- or plastic-columns column or on a Biotage Horizon system. HPLC separations were performed on a Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm or on a Waters Delta Prep Systems using Kromasil C8, 10 µm columns. Reactions performed in a microwave reactor were performed in a Personal Chemistry Smith Creator, Smith synthesizer or an Emrys Optimizer.

List of used abbreviations:

Abbreviation	Explanation
AcOH	Acetic acid
Aq	Aqueous
br	Broad
Brine	A saturated solution of sodium chloride in water
BSA	Bovine Serum Albumine

CDI	Carbonyldiimidazole
d	Doublet
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIEA	N,N-Diisopropylethylamine
DIPEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	N,N-dimethylpyridin-4-amine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulphoxide
EDCI	N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride
EtOAc	Ethyl acetate
EtOH	Ethanol
HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluromium hexafluorophosphate
HEPES	[4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HFA	Hydrofluoroalkanes
HOAc	Acetic acid
HOBT	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
Hz	Hertz
J	Coupling constant
LDA	Litiumdiisopropyl amide
M	Multiplet
m-CPBA	3-chlorobenzenecarboperoxoic acid
MeOH	Methanol
MHz	Megahertz
mL	Millilitre
MS	Mass spectra

NBS	1-Bromopyrrolidine-2,5-dione(N-bromo succinimide)
NCS	1-chloropyrrolidine-2,5-dione
q	Quartet
r.t.	Room temperature
s	Singlet
SMOPS	sodium 3-methoxy-3-oxopropane-1-sulfinate
t	triplet
TB	Tyrodes Buffer
TBTU	N-[(1H-1,2,3-benzotriazol-1-yloxy)(dimethylamino)methylene]-N-methylmethanaminium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane

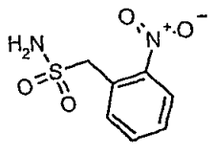
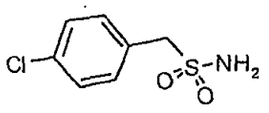
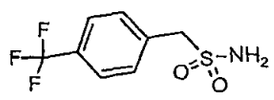
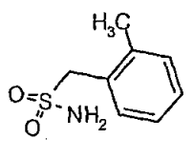
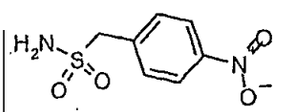
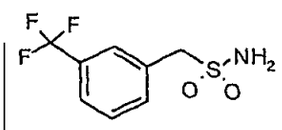
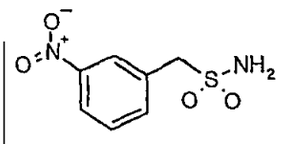
Sulphone amides

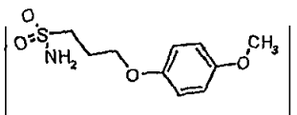
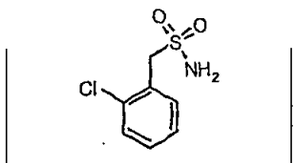
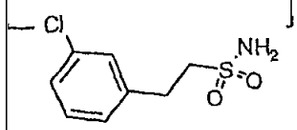
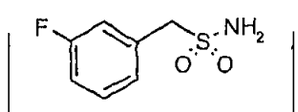
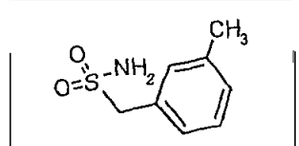
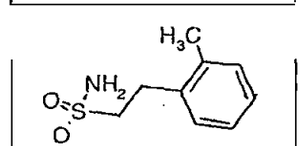
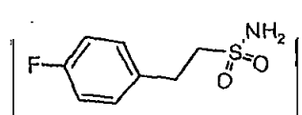
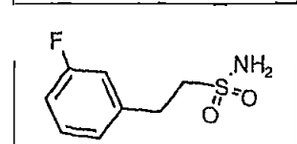
Synthesis of sulfone amides

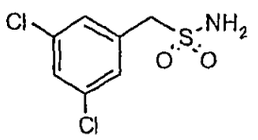
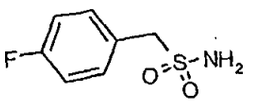
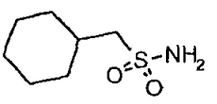
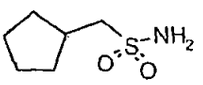
Each of the following substances was made by reacting the corresponding sulfonyl chloride (0.75 mmol) with a saturated solution of ammonia in MeOH (5 mL). After evaporation of the ammonia and MeOH the residues were dissolved in MeOH (5 mL) and to a few samples DMF (2 mL) was also added to dissolve the reaction mixtures. The solutions where then separately filtered through ISOLUTE SCX-2, (25 mL cartridge) containing acidic ion exchange resin (propylsulphonic acid type, 5 g). MeOH (16 mL) was used to rinse the product from the resin. After removal of the solvent each of the products were used without further purification as described in Method A below.

The sulfonamides made by this procedure are listed in table 1. Other sulphone amides were made *via* methods described in the examples or methods similar to those described.

Table 1

Products	Compound name	Mw	Crude yield	
			mg	%
	1-(2-nitrophenyl)methanesulfonamide	216.22	222	134%
	1-(4-chlorophenyl)methanesulfonamide	205.66	212	129%
	1-[4-(trifluoromethyl)phenyl]methanesulfonamide	239.22	114	123%
	1-(2-methylphenyl)methanesulfonamide	185.25	10	7%
	1-(4-nitrophenyl)methanesulfonamide	216.22	198	119%
	1-[3-(trifluoromethyl)phenyl]methanesulfonamide	239.22	210	114%
	1-(3-nitrophenyl)methanesulfonamide	216.22	194	118%

	3-(4-methoxyphenoxy)propane-1-sulfonamide	245.30	210	113%
	1-(2-chlorophenyl)methanesulfonamide	205.66	200	122%
	2-(3-chlorophenyl)ethanesulfonamide	219.69	204	119%
	1-(3-fluorophenyl)methanesulfonamide	189.21	192	130%
	1-(3-methylphenyl)methanesulfonamide	185.25	284	196%
	2-(2-methylphenyl)ethanesulfonamide	199.27	324	185%
	2-(4-fluorophenyl)ethanesulfonamide	203.24	164	106%
	2-(3-fluorophenyl)ethanesulfonamide	203.24	176	111%

	1-(3,5-dichlorophenyl)methanesulfonamide	240.11	192	109%
	1-(4-fluorophenyl)methanesulfonamide	189.21	156	108%
	1-cyclohexylmethanesulfonamide	177.27	134	95%
	1-cyclopentylmethanesulfonamide	163.24	148	108%

Synthesis of examples

Method A:

1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid (See Example 1(d)) (1 Eq), sulfone amide (1.48 Eq, the amount and structure of the sulfonamide used is specified in each of the examples below) and DIPEA (5 Eq) was stirred in DMF (8 mL/mmol of the acid used). HATU (1.05 Eq) was dissolved in DMF (4 mL/mmol of the acid used) added and the reaction was stirred at r.t over night. The solvent was removed in vaccuo and the crude reaction mixture was dissolved in DMSO (1 mL) and purified by preparative HPLC (Kromasil C8, 5µm particles, 100x21.2mm column, Eluent A: 100% acetonitrile, Eluent B: 0,1M ammonium acetate in water containing 5% acetonitrile, flow 30 mL / min, using a increasing gradient of acetonitrile over 8 minutes to afford the products after evaporation of the solvents).

Method B

To a solution of 1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.21mmol) or 1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (0.21 mmol) DCM (2mL) was added TBTU 0.25 mmol) and DIPEA (1.05) mmol. The reaction mixture was stirred for 10 minutes followed by addition of sulfoneamide (0.25 mmol) e.g. 5-chlorothiophene-3-sulfonamide. The reaction mixture was stirred over night followed by addition of 0.1 M $KHSO_4$ (2mL), the organic phase was isolated and the crude reaction mixture was submitted to preparative HPLC (see below for details) in order to isolate the wanted product, e.g. ethyl 6-[4-({[(5-chloro-3-thienyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate.
The preparative HPLC system used was a Waters Fraction Lynx Purification System with Kromasil C8 5mm 20x100 mm columns. The mobile phase used was varying gradients of CH_3CN and 0.1 M NH_4OAc(aq) buffer. The flow was 30 mL/minute. MS triggered fraction collection was used. Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass Quattro micro, both equipped with a pneumatically assisted electro spray interface.

Method C

A solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (0.091 g, 0.3 mmol), DIPEA 0.074 g, 0.6 mmol) and TBTU (0.039 g, 0.3 mmol) in 1eq. DCM/ 1 eq .DMF (2 mL) was added to sulfonamide(0.4 mmol), e.g. 4-(trifluoromethyl)benzenesulfonamide. The reaction mixture was stirred for 48h followed by addition of TBTU (0.013 g, 0.1 mmol). After 20h the solvents were removed *in vacuo*. The crude reaction mixture was added $NaHSO_4$ (2 mL, 1M) and due to differences in solubility between products DCM and DCM/ethyl acetate was used for extraction. The organic phase was isolated and the solvents were removed *in vacuo*. The crude material was purified using preparative HPLC (see below for details) in order to isolate the desired product, e.g. isopropyl 5-cyano-2-methyl-6-{3-[({[4-(trifluoromethyl)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate.

Example 1

5-Cyano-6-[3-(2-methoxycarbonyl-phenylmethanesulfonylaminocarbonyl)-az

etidin-1-yl]-2-methyl-nicotinic acid ethyl ester

(a) Ethyl 2-((dimethylamino)methylene)-3-oxobutanoate

1,1-dimethoxy-N,N-dimethylmethanamine (500 g, 4195 mmol) was added to ethyl 3-oxobutanoate (461.6 g, 3547 mmol) under an atmosphere of nitrogen at r.t during 13 minutes(weak exotherm). The orange red solution was stirred for 22 hours and concentrated in vaccuo. The residue was co-evaporated with toluene (3 times 200 ml each) and used without no need for further purification in the next step.

MS $^{m}/_{z}$: 186 (M+1).

(b) Ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

Sodium ethoxide (1240.7 g of a 21 wt % solution in EtOH, 3829 mmol) was added to a stirred suspension of 2-cyanoacetamide (298 g, 3544 mmol) in EtOH (3000 mL) during 8 minutes under an atmosphere of nitrogen at r.t. The crude condensation product from step (a) above dissolved in 950 ml EtOH was added slowly (slightly exothermic reaction) and after about one third had been added further EtOH (1000 mL) was added to allow efficient stirring (suspension) followed by the addition of the rest of the condensation product (total addition time 30 min). After stirring over night at r.t. HOAc (526 g, 8759 mmol) was added to the reaction and the mixture was concentrated in vaccuo leaving a thick orange slurry (volume about 3000 mL), 1 M HCl (4628 mL, 4628 mmol) was added during 10 min followed by water (500 mL). The stirring was stopped and the precipitate was filtered off and washed with water (200 mL). NMR showed the presence of about 5-10 % of the corresponding acid and the solid was washed by stirring with further water (1500 mL + 3 x 1000 mL), a solution of saturated $NaHCO_3$ (400 mL) in water (600 mL) and finally water (1000 mL). Filtration of the solid and drying in vaccuo at 80 °C gave pure ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate. Yield: 493 g (67 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (3H, t, J = 7.1 Hz), 2.62 (3H, s), 4.25 (2H, q, J = 7.1 Hz), 8.71 (1H, s), 12.79 (1H, br s).

(c) Ethyl 6-chloro-5-cyano-2-methylnicotinate

Toluene (4000 mL) and thionylchloride (507 g, 4262 mmol) were added to ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (293 g, 1421 mmol) under an atmosphere of nitrogen and the mixture was heated to 50 °C (oil bath temperature) and DMF (100 g, 1368 mmol) was added during 2 minutes. The temperature was raised to 80 °C (oil bath temperature) and the stirring was continued for 2 hours. The mixture was concentrated in vaccuo (about 3500 ml was evaporated off) leaving a red oil. EtOH (1000 mL, 99%) was added and then evaporated off. Dichloromethane (4000 mL) was added followed by 4 % $NaHCO_3$ solution (4000 mL) and the mixture was stirred for 15 minutes. The organic phase was separated and evaporated to give ethyl 6-chloro-5-cyano-2-methylnicotinate as a dark red crude solid which was used without further purification. Yield: 301 g (75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, J = 7.1 Hz), 2.91 (3H, s), 4.40 (2H, q, J = 7.1 Hz), 8.49 (1H, s).

(d) 1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid

Ethyl 6-chloro-5-cyano-2-methylnicotinate (50.98 g, 227 mmol), azetidine-3-carboxylic acid (24.09 g, 238 mmol) and DIPEA (118.9 mL, 681 mmol) were suspended in EtOH (250 mL) and heated at reflux for 1 h. The reaction mixture was cooled to r.t and added drop-wise to $KHSO_4$ (154.5 g, 1135 mmol) in water (3000 mL). The solids were collected by filtration and dried under vacuum to afford 1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid as a solid, which was used without further purification. Yield: 65.33 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.72 (3H, s), 3.59-3.68 (1H, m), 4.31 (2H, q, J = 7.1 Hz), 4.55-4.68 (4H, m), 8.28 (1H, s).

MS $^m/_z$: 290 (M+1).

(e) 5-Cyano-6-[3-(2-methoxycarbonyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid (0.072 g, 0.25 mmol), methyl 2-[(aminosulfonyl)methyl]benzoate (0.085 g, 0.375 mmol) and triethyl amine (0.55 mL, 4 mmol) was stirred in DMF (2 mL). HATU (0.100 g, 0.263 mmol) dissolved in DMF (1 mL) was added and the reaction was stirred at r.t over night. The

reaction mixture was purified by preparative HPLC using Kromasil C8, 5µ particles, 100x21.2mm colonn, Eluent A: 100% acetonitrile, Eluent B: 95% 0,1M ammonium acetate, 5% acetonitrile flow 30 mL / min, gradien 25% A to 75% A in 8 minutes to afford 5-cyano-6-[3-(2-methoxycarbonyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester as a solid. Yield: 0.063 g (50%).

^{1}H NMR (400 MHz, DMSO-d_6) 1.26 (t, J = 7.2 Hz, 3H), 2.59 (s, 3H), 3.30 (m, 1H overlapped by water), 3.76 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 4.27 (t, J = 2.6 Hz, 2H), 4.35 (t, J = 4.3 Hz, 2H), 5.12 (s, 2H), 7.40 (d, J = 7.3 Hz, 1H), 7.48 (t, J = 3.9 Hz, 1H), 7.55 (t, J = 7.1 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 8.26 (s, 1H)

MS $^m/_z$: 501 (M+1)

Example 2

6-[3-({[(3-Bromobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (0.257 g, 0.89 mmol), 1-(3-bromophenyl)methanesulfonamide (0.223 g, 0.89 mmol) and TEA (0.360 g, 3.6 mmol) was stirred in DMF (5 mL). HATU (0.405 g, 1.07 mmol) was added and reaction mixture was stirred at r.t for 3.5 h. An additional amount of HATU (0.073 g, 0.18 mmol) was added and the stirring was continued for 18 h. The DMF was evaporated and the residue was dissolved in EtOAc (80 mL). The organic phase was washed with NH_4Cl(sat,aq) (2 x 8 mL), water (5 mL), dried ($MgSO_4$), filtered and evaporated to afford 0.658 g of the crude product as a solid. Purification by flash chromatography gave 0.429 g of the product which was about 90 % pure according to LC-MS. Further purification of this material was done by preparative HPLC (Kromasil C8 10µm 250 mm x 50 id. Eluent A: 100 % acetonitrile, Eluent B: 95 % 0.1M aq. ammonium acetate and 5 % acetonitrile. Conditions used: Flow 50 mL / minutes, a linear gradient from 0 % A to 100 % A during 42 minutes was used). The product precipitated during the evaporation of the solvent and was filtered off and washed with water. This afforded the pure product as a white solid. Yield: 0.181 g (39 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (t, J= 7..0 Hz, 3H), 2.62 (s, 3H), 3.56 (m, 1H), 4.23 (q, J= 7.0 Hz, 2H), 4.25-4.31 (m, 2H), 4.41 (m, 2H), 4.78 (s, 2H), 7.34 (m, 2H), 7.53 (s, 1H), 7.56-7.62 (m, 1H), 8.30 (s, 1H), 11.88 (s, 1H).

MS $^m/_z$: 522 (M+1).

Example 3

5-Cyano-2-methyl-6-[3-(2-nitro-phenylmethanesulfonylaminocarbonyl)-zetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 1-(2-nitrophenyl)methanesulfonamide (0.111 g crude, 0.37 mmol).Yield: 0.031 g (25%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.5 (m, 1H, overlapped by water), 4.18 (q, J = 7.1 Hz, 2H), 4.26 (t, J = 3.1 Hz, 2H), 4.34 (t, J = 4.2 Hz, 2H), 5.04 (s, 2H), 7.51 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.3 Hz, 1H), 7.66 (t, J = 6.9 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.24 (s, 1H)
MS $^m/_z$: 488 (M+1)

Example 4

6-[3-(2-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using using 1-(2-chlorophenyl)methanesulfonamide (0.100 g crude, 0.37 mmol).Yield: 0.031 g (25%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.52 (m, 1H, overlapped by water), 4.18 (q, J = 7.1 Hz, 2H), 4.30 (t, J = 7.4 Hz, 2H), 4.40 (t, J = 9.4 Hz, 2H), 4.81 (s, 2H), 7.31 - 7.38 (m, 2H), 7.44 (m, 2H), 8.25 (s, 1H)
MS $^m/_z$: 477 (M+1)

Example 5

6-[3-(4-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-(4-chlorophenyl)methanesulfonamide (0.106 g crude, 0.37 mmol).Yield: 0.057 g (48%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.58 (s, 3H), 3.45 (m, 1H, overlapped by water), 4.18 (q, J = 7.1 Hz, 2H), 4.23 (m, 2H), 4.36 (t, J = 8.6 Hz, 2H), 4.65 (s, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 8.25 (s, 1H)
MS $^m/_z$: 477 (M+1)

Example 6

5-Cyano-2-methyl-6-[3-(4-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 1-[4-(trifluoromethyl)phenyl]methanesulfonamide (0.057g crude, 0.23 mmol).Yield: 0.050 g (39%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.49 (m, 1H, overlapped by water), 4.2 (q, J = 7.1 Hz, 2H), 4.24 (m, 2H), 4.36 (t, J = 8.8 Hz, 2H), 4.75 (s, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 8.24 (s, 1H)
MS $^m/_z$: 511 (M+1)

Example 7

5-Cyano-6-[3-(3-fluoro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-(3-fluorophenyl)methanesulfonamide (0.095 g crude, 0.37 mmol).Yield: 0.065 g (56%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.48 (m, 1H, overlapped by water), 4.23 - 4.15 (m, 4H), 4.36 (t, J = 9.1 Hz, 2H), 4.69 (s, 2H), 7.18 - 7.09 (m, 3H), 7.36 (q, J = 7.5 Hz, 1H), 8.24 (s, 1H)
MS $^m/_z$: 461 (M+1)

Example 8

5-Cyano-2-methyl-6-[3-(3-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 1-[3-(trifluoromethyl)phenyl]methanesulfonamide (0.105 g crude, 0.37 mmol).Yield: 0.050 g (39%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.48 (m, 1H), 4.18 (m, 4H), 4.35 (t, J = 8.8 Hz, 2H), 4.78 (s, 2H), 7.57 (m, 3H), 7.69 (d, J = 6.6 Hz, 1H), 8.24 (s, 1H)

MS $^m/_z$: 511 (M+1)

Example 9

6-[3-(3-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-(3-chlorophenyl)methanesulfonamide (0.096 g crude, 0.37 mmol).Yield: 0.050 g (42%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.46 (m, 1H overlapped by water), 4.23 - 4.15 (m, 4H), 4.35 (d, J = 9.3 Hz, 2H), 4.68 (s, 2H), 7.24 (d, J = 7.3 Hz, 1H), 7.38 - 7.31 (m, 3H), 8.24 (s, 1H)

MS $^m/_z$: 477 (M+1)

Example 10

6-{3-[2-(3-Chloro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-5-cyano-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 2-(3-chlorophenyl)ethanesulfonamide (0.102 g crude, 0.37 mmol).Yield: 0.055 g (45%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 2.98 (t, J = 7.5 Hz, 2H), 3.45 (m, 2H), 3.8-3.5 (m, 2H overlapped by water), 4.17 (m, 3H), 4.34 (t, J = 8.5 Hz, 2H), 7.17 (d, J = 7.1 Hz, 2H), 7.29 - 7.24 (m, 2H), 8.23 (s, 1H)

MS $^m/_z$: 491 (M+1)

Example 11

5-Cyano-2-methyl-6-[3-(4-nitro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 1-(4-nitrophenyl)methanesulfonamide (0.099 g crude, 0.37 mmol).Yield: 0.032 g (26%) .

1H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 7.2 Hz, 3H), 2.56 (s, 3H), 3.44 (m, 1H), 4.18 (m, 4H), 4.33 (t, J = 8.4 Hz, 2H), 4.79 (s, 2H), 7.56 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H), 8.23 (s, 1H)

MS $^m/_z$: 488 (M+1)

Example 12

5-Cyano-2-methyl-6-[3-(2-phenyl-ethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 2-phenylethanesulfonamide (0.078 g crude, 0.37).Yield: 0.044 g (39%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.55 (s, 3H), 2.95 (t, J = 7.7 Hz, 2H), 3.45 (m, 1H), 4.17 (q, J = 7.1 Hz, 4H), 4.34 (t, J = 8.6 Hz, 2H), 7.25 - 7.12 (m, 5H), 8.23 (s, 1H) (The two protons next to the sulfone are overlapping with the DMSO signal)

MS $^m/_z$: 457 (M+1)

Example 13

5-Cyano-2-methyl-6-(3-o-tolylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

Prepared according to method A using 1-(2-methylphenyl)methanesulfonamide (0.010 g crude, 0.05mmol).Yield: 0.002 g (2%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.2 Hz, 3H), 2.32 (s, 3H), 2.57 (s, 3H), 3.4 (m, 1H overlapped by water), 4.18 (m, 2H), 4.30 (m, 2H), 4.39 (m, 2H), 4.63 (s, 2H), 7.15 (m, 4H), 8.24 (s, 1H)

MS $^m/_z$: 457 (M+1)

Example 14

5-Cyano-2-methyl-6-[3-(3-nitro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 1-(3-nitrophenyl)methanesulfonamide (0.097 g crude, 0.37 mmol).Yield: 0.055 g (45%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.2 Hz, 3H), 2.57 (s, 3H), 3.46 (m, 1H), 4.18 (m, 4H), 4.32 (t, J = 9.2 Hz, 2H), 4.82 (s, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 8.10 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H)

MS $^m/_z$: 488 (M+1)

Example 15

5-Cyano-6-{3-[2-(4-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 2-(4-fluorophenyl)ethanesulfonamide (0.082 g crude, 0.37 mmol).Yield: 0.051 g (43%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.55 (s, 3H), 2.95 (t, J = 7.6 Hz, 2H), 3.48 (m, 1H), 3.70 - 3.50 (m, 2H), 4.17 (q, J = 7.2 Hz, 4H), 4.36 (t, J = 9.0 Hz, 2H), 7.04 (t, J = 8.9 Hz, 2H), 7.24 (dd, J = 8.6, 5.5 Hz, 2H), 8.23 (s, 1H)

MS $^m/_z$: 475 (M+1)

Example 16

5-Cyano-2-methyl-6-[3-(2-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

Prepared according to method A using 1-[2-(trifluoromethyl)phenyl]methanesulfonamide (0.100 g crude, 0.37 mmol).Yield: 0.045 g (35 %).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.58 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.31 (t, J = 6.9 Hz, 2H), 4.41 (t, J = 8.8 Hz, 2H), 4.83 (s, 2H), 7.68 - 7.54 (m, 3H), 7.74 (d, J = 8.1 Hz, 1H), 8.24 (s, 1H)

MS $^m/_z$: 511 (M+1)

Example 17

5-Cyano-6-[3-(4-fluoro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-(4-fluorophenyl)methanesulfonamide (0.078 g crude, 0.37 mmol).Yield: 0.050 g (43%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.49 (m, 1H), 4.20 (m, 4H), 4.36 (t, J = 9.0 Hz, 2H), 4.65 (s, 2H), 7.13 (t, J = 8.8 Hz, 2H), 7.32 (dd, J = 8.6, 5.5 Hz, 2H), 8.25 (s, 1H)

MS $^m/_z$: 461 (M+1)

Example 18

5-Cyano-6-(3-cyclopentylmethanesulfonylaminocarbonyl-azetidin-1-yl)-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-cyclopentylmethanesulfonamide (0.074 g crude, 0.37 mmol).Yield: 0.013 g (12%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.21 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.44 (m, 2H), 1.52 (m, 2H), 1.79 (m, 2H), 2.13 (m, 1H), 2.56 (s, 3H), 3.38 (d, J = 6.8 Hz, 2H), 3.51 (m, 1H overlapped by water), 4.17 (q, J = 7.1 Hz, 2H), 4.29 (m, 2H), 4.41 (t, J = 9.0 Hz, 2H), 8.23 (s, 1H)

MS $^m/_z$: 435.0 (M+1)

Example 19

5-Cyano-6-{3-[2-(2-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 2-(2-fluorophenyl)ethanesulfonamide (0.084 g crude, 0.37 mmol).Yield: 0.060 g (51%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 2.99 (t, J = 7.7 Hz, 2H), 3.46 (m, 1H owerlapped by water), 3.67 - 3.54 (m, 2H owerlapped by water), 4.17 (m, 4H), 4.36 (t, J = 8.8 Hz, 2H), 7.08 (t, J = 8.0 Hz, 2H), 7.21 (m, 1H), 7.30 (t, J = 7.7 Hz, 1H),8.23 (s, 1H)

MS $^m/_z$: 475 (M+1)

Example 20

5-Cyano-6-[3-(3,5-dichloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-(3,5-dichlorophenyl)methanesulfonamide (0.181 g crude, 0.37 mmol).Yield: 0.053 g (41%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.56 (s, 3H), 3.47 (m, 1H), 4.18 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.35 (t, J = 9 Hz, 2H), 4.69 (s, 2H), 7.30 (s, 2H), 7.55 (s, 1H), 8.23 (s, 1H)

MS $^m/_z$: 511 (M+1)

Example 21

5-Cyano-6-(3-cyclohexylmethanesulfonylaminocarbonyl-azetidin-1-yl)-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-cyclohexylmethanesulfonamide (0.065 g crude, 0.37 mmol).Yield: 0.012 g (11%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 0.98-1.25 (m, 8H), 1.60 - 1.50 (m, 3H), 1.74 (m, 3H), 2.55 (s, 3H), 3.26 (d, J = 6.0 Hz, 2H), 3.58 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.28 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 8.7 Hz, 2H), 8.23 (s, 1H)

MS $^m/_z$: 449 (M+1)

Example 22

5-Cyano-6-{3-[2-(3-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 2-(3-fluorophenyl)ethanesulfonamide (0.088 g crude, 0.37 mmol).Yield: 0.044 g (37%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 2.98 (t, J = 7.7 Hz, 2H), 3.45 (m, 1H owerlapped by water), 3.69 - 3.56 (m, 2H owerlapped by water), 4.17 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.35 (t, J = 8.9 Hz, 2H), 6.95 (m, 1H), 7.06 (m, 2H), 7.27 (dd, J = 14.4, 8.0 Hz, 1H), 8.23 (s, 1H)

MS $^m/_z$: 475 (M+1)

Example 23

6-[3-(Benzo[d]isoxazol-3-ylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

Prepared according to method A using 1-(1,2-benzisoxazol-3-yl)methanesulfonamide (0.080 g, 0.37 mmol).Yield: 0.035 g (28%) .

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (t, J = 7.1 Hz, 3H), 2.58 (s, 3H), 3.27 (m, 1H overlapped by water), 4.20 (q, J = 7.1 Hz, 2H), 4.84 (s, 2H), 4.27 (m, 4H), 7.28 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 8.24 (s, 1H)
MS $^m/_z$: 484 (M+1)

Example 24

1-[4-Amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]-*N*-(benzylsulfonyl)piperidine-4-carboxamide

(a) 5,6-Dichloro-N-(2-hydroxybutyl)nicotinamide

5,6-Dichloronicotinic acid (20.0 g, 104 mmol), EDCI (26.0 g, 135 mmol) and HOBt (18.3 g, 135 mmol) were dissolved in DCM (500 mL) at r.t. The reaction mixture was stirred at r.t for 90 minutes and then 1-aminobutan-2-ol (15.0 g, 156 mmol) and DIPEA (54.4 mL, 313 mmol) were added. The reaction mixture was stirred at r.t for 18 h. The reaction mixture was diluted with DCM (400 mL) and the combined organics were washed with saturated NH_4Cl (2 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford 5,6-dichloro-N-(2-hydroxybutyl)nicotinamide as a solid, which was used crude assuming a 100% conversion.

(b) 5,6-Dichloro-N-(2-oxobutyl)nicotinamide

Oxalyl Chloride (16.3 mL, 187 mmol) was dissolved in DCM (500 mL) and cooled to -78 °C. DMSO (26.3 mL, 374 mmol) was added drop-wise and stirred at -78 °C for 10 minutes. 5,6-Dichloro-N-(2-hydroxybutyl)nicotinamide (30 g, 94 mmol) was dissolved in DCM / DMSO (3:1) and added slowly to the solution. The solution was stirred at -78 °C for 30 minutes. TEA (65.2 mL, 467 mmol) was added to the solution and stirred for 30 minutes. The solution was warmed to r.t and stirred for 3 h. The reaction mixture was diluted with DCM (200 mL) and the combined organics were washed with water (2 x 200 mL), brine (2 x 200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford 5,6-dichloro-N-(2-oxobutyl)nicotinamide as a solid, which was used crude assuming a 100% conversion.

(c) 2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridine

5,6-Dichloro-N-(2-oxobutyl)nicotinamide (26.7 g, 78 mmol) and $POCl_3$ (59.6 g, 389 mmol) were dissolved in DMF (500 mL) and heated at 90 °C for 30 minutes. The reaction mixture was poured onto ice. Solid $NaHCO_3$ was added in portions until the pH was raised to pH > 8. The reaction mixture was diluted with water (500 mL) and the combined aqueous were washed with EtOAc (3 x 400 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (EtOAc/hexanes, 1/9) gave 2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridine as a solid. Yield: 7.08 g (37.5 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (2H, t, J = 7.5 Hz), 2.78 (2H, q, J = 7.5 Hz), 6.91 (1H, s), 8.35 (1H, d, J = 1.9 Hz) 8.29 (1H, d, J = 1.9 Hz).

MS $^m/_z$: 244 (M+1).

(d) 2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylthio)pyridine

n-Butyllithium (2.5 M in hexanes, 7.14 mL, 17 mmol) was added drop-wise to diisopropylamine (2.62 mL, 19 mmol) in THF (5 mL) at 0 °C. The solution was stirred at 0 °C for 30 minutes and then cooled to -78 °C. 2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridine (3.50 g, 14 mmol) in THF (30 mL) was added to the solution and the reaction was stirred at -78 °C for 1 h. S-methyl methanesulfonothioate (1.77 mL, 19 mmol) was added and the solution warmed to r.t. The reaction mixture was stirred for 16 h. The reaction mixture was diluted with saturated NH_4Cl (100 mL). The solution was washed with EtOAc (3 x 50 mL). The combined organics were washed with brine (1 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (15% EtOAc/hexanes to 20% EtOAc/hexanes) gave 2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylthio)pyridine as a solid. Yield: 2.71 g (65.1 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (2H, t, J = 7.6 Hz), 2.35 (3H, s), 2.79 (2H, q, J = 7.6 Hz), 6.98 (1H, s), 8.58 (1H, s).

MS $^m/_z$: 290 (M+1).

(e) Methyl 1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylthio)pyridin-2-yl]piperidine-4-carboxylate

2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylthio)pyridine (3.11 g, 11 mmol), methyl piperidine-4-carboxylate (2.00 g, 14 mmol) and DIPEA (3.75 mL, 22 mmol) were dissolved in DMA (50 mL) and heated to 120 °C for 2h. The reaction mixture was cooled to r.t and concentrated under reduced pressure. The crude material was dissolved in EtOAc (100 mL),

washed with NH_4Cl (2 x 60 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (1:5 EtOAc/hexanes to 1:3 EtOAc/hexanes) gave methyl 1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylthio)pyridin-2-yl]piperidine-4-carboxylate as a solid. Yield: 4.26 g (87.6 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (2H, t, J = 7.6 Hz), 1.88-2.06 (4H, m), 2.32 (3H, s), 2.51-2.58 (1H, m), 2.76 (3H, q, J = 7.6 Hz), 2.93-2.99 (2H, m), 3.72 (3H, s), 3.81-3.92 (2H, m), 6.91 (1H, s), 8.43 (1H, s).

MS $^m/_z$: 396 (M+1).

(f) Methyl 1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylsulfinyl)pyridin-2-yl]piperidine-4-carboxylate

Methyl 1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylthio)pyridin-2-yl]piperidine-4-carboxylate (2.12 g, 5.4 mmol) was dissolved in DMF (500 mL) and 3-chlorobenzenecarboperoxoic acid (2.64 g, 10.7 mmol) was slowly added at r.t. The solution was stirred at r.t for 4 h. 3-chlorobenzenecarboperoxoic acid (1.32 g, 5.35 mmol) was slowly added at r.t for 3 h. Saturated $Na_2S_2O_3$ (30 mL) was added and the solution was stirred for 5 minutes. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and the combined organics were separated and washed with NaOH (1M, 2 x 40 mL), brine (1 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (1:2 EtOAc/hexanes) gave methyl 1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylsulfinyl)pyridin-2-yl]piperidine-4-carboxylate as a solid. Yield: 2.71 g (65.1 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (1H, t, J = 7.5 Hz), 1.83-2.08 (4H, m) 2.52-2.61 (1H, m), 2.75 (2H, q, J = 7.5Hz), 2.93-3.00 (1H, m), 3.04-3.13 (1H, m), 3.23 (3H, s), 3.72 (3H, s), 3.86-4.01 (2H, m), 6.87 (1H, s), 8.51 (1H, s).

MS $^m/_z$: 412 (M+1).

(g) Methyl 1-[4-azido-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylate

Methyl 1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-4-(methylsulfinyl)pyridin-2-yl]piperidine-4-carboxylate (0.150 g, 0.36 mmol) and sodium azide (0.026 g, 0.40 mmol) were dissolved in DMA (1 mL) and stirred at r.t for 48 h. The reaction mixture was diluted with EtOAc (40 mL) and the combined organics were separated and washed with water (2 x 40 mL), brine (1 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford methyl 1-[4-

azido-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylate as a solid, which was used crude assuming a 100% conversion.

(h) Methyl 1-[4-amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylate

Methyl 1-[4-azido-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylate (0.150 g, 0.36 mmol) was dissolved in THF (0.90 mL) and cooled to 0 °C. Zinc dust (0.109 g, 1.66 mmol) was added. NH_4Cl (0.900 mL) was added slowly to the solution. The solution was warmed to r.t for 1.5 h. The reaction mixture was filtered (celite) and diluted with EtOAc (40 mL) and the combined organics were washed with saturated with NH_4OAc (2 x 30 mL), brine (1 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford methyl 1-[4-amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylate as a solid, which was used crude assuming a 100% conversion.

(i) 1-[4-Amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylic acid

Methyl 1-[4-amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylate (0.045 g, 0.123 mmol), and lithium hydroxide (2 M, 1.23 mL, 2.46 mmol) were suspended in THF (1 mL) and stirred at r.t for 16 h. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The solution was washed with EtOAc (3 x 40 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 1-[4-amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylic acid as a solid, which was used crude assuming a 100% yield.

(j) 1-[4-Amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]-*N*-(benzylsulfonyl)piperidine-4-carboxamide

1-[4-amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxylic acid (0.040 g, 0.11 mmol), EDCI (0.026 g, 0.14 mmol) and HOBt (0.019 g, 0.14 mmol) were dissolved in DCM (2 mL) at r.t. The reaction mixture was stirred at r.t for 30 minutes and then 1-phenylmethanesulfonamide (0.023 g, 0.14 mmol) and DIPEA (0.099 mL, 0.57 mmol) were added. The reaction mixture was stirred at r.t for 48 h. The reaction mixture was diluted with EtOAc (50 mL). The combined organics were washed with saturated NH_4Cl (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product.

Flash chromatography (EtOAc/hexanes 5/1 to EtOAc/hexanes 5/1 with 0.5% AcOH) gave 1-[4-amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]-*N*-(benzylsulfonyl)piperidine-4-carboxamide as a solid. Yield: 0.018 g (30.5 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24-1.33 (6H, m), 1.85-1.93 (4H, m), 2.26-2.35 (1H, m), 2.71-2.88 (4H, m), 3.80-3.89 (2H, m), 4.69 (2H, s), 6.81 (1H, s), 7.35-7.44 (5H, m), 8.52 (1H, s).

MS $^m/_z$: 505 (M+1).

Example 25

4-Amino-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloronicotic acid ethyl ester

(a) Ethyl 4-azido-5,6-dichloronicotinate

4,5,6-Trichloronicotinic acid (1.28 g, 5.65 mmol) and sodium azide (0.370 g, 5.69 mmol) were dissolved in DMA (10 mL) and stirred at r.t for 16h. Iodoethane (0.670 mL, 6.60 mmol) and potassium carbonate (3.90 g, 28.25 mmol) were added to the reaction mixture and stirred at r.t for 16 h. The reaction mixture was diluted with EtOAc (40 mL) and the combined organics were washed with water (2 x 40 mL), brine (1 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield ethyl 4-azido-5,6-dichloronicotinate as a solid, which was used crude assuming 100% conversion

(b) Ethyl 4-amino-5,6-dichloronicotinate

Ethyl 4-azido-5,6-dichloronicotinate (0.700 g, 2.68 mmol) was dissolved in 1:1 THF/MeOH (10 mL). Zinc dust (0.109 g, 1.66 mmol) was added and the solution was cooled to 5 °C. NH_4Cl (2 mL) was added slowly to the solution. The solution was warmed to r.t for 2 h. The reaction mixture was filtered (celite), washed with MeOH (50 mL) and concentrated to yield ethyl 4-amino-5,6-dichloronicotinate as a solid, which was used crude assuming a 100% conversion

(c) 1-[4-Amino-3-chloro-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid

Ethyl 4-amino-5,6-dichloronic (0.320 g, 1.36 mmol), piperidine 4-carboxylic cid (0.352 g, 2.72 mmol) and DIPEA (11.9 mL, 68.2 mmol) were dissolved in DMA (2.5 mL) and heated at 120 °C for 2h. The reaction mixture was cooled to r.t and concentrated under reduced

pressure. The crude material was dissolved in EtOAc (40 mL), washed with NH_4Cl (1 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (EtOAc/hexanes 1/3 to EtOAc/hexanes 2/3 with 0.5 % AcOH) gave 1-[4-amino-3-chloro-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid as a solid. Yield: 0.154 g (34.5 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (2H, t, J = 7.1 Hz), 1.88-2.07 (4H, m), 2.55-2.62 (1H, m), 2.92-3.01 (2H, m), 3.87-3.90 (2H, m), 4.33 (3H, q, J = 7.1 Hz), 8.60 (1H, s).

MS $^m/_z$: 328 (M+1).

(d) 4-Amino-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloronicotic acid ethyl ester

1-[4-Amino-3-chloro-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid (0.070 g, 0.21 mmol), EDCI (0.053 g, 0.28 mmol) and HOBt (0.038 g, 0.28 mmol) were dissolved in DCM (5 mL) at r.t. The reaction mixture was stirred at r.t for 30 minutes and then 1-phenylmethanesulfonamide (0.051 g, 0.30 mmol) and DIPEA (0.22 mL, 1.3 mmol) were added. The reaction mixture was stirred at r.t until complete consumption of starting material was observed by HPLC analysis. The reaction mixture was diluted with DCM (30 mL) and washed with saturated NH_4Cl (2 x 30 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (3:7 EtOAc/hexanes then 3:7 EtOAc/hexanes with 0.5 % AcOH) 4-amino-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloronicotic acid ethyl ester as a solid. Yield: 0.079 g (77 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.4 Hz), 1.83-1.88 (4H, m), 2.28-2.36 (1H, m), 2.81-2.88 (2H, m), 3.92-3.95 (2H, m), 4.33 (2H, q, J = 7.4 Hz), 4.69 (4H, s), 7.35-7.41 (5H, m), 8.59 (1H, s).

MS $^m/_z$: 481 (M+1).

Example 26

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid isopropyl ester

(a) 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid

Ethyl 6-(3-(tert-butoxycarbonyl)azetidin-1-yl)-5-cyano-2-methylnicotinate (1.50 g, 4.16 mmol), and lithium hydroxide (3.00 g, 8.32 mmol) were suspended in MeOH (40 mL) and

heated at 90 °C for 1 h. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The precipitate was filtered and collected. The mother liquor was washed with EtOAc (1 x 60 mL), dried ($MgSO_4$), concentrated under reduced pressure and combined with the solid to afford 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid as a solid, which was used crude.

(b) Isopropyl 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinate

6-{3-[(*tert*-Butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid (0.400 g, 1.20 mmol), 2-iodopropane (0.181 mL, 1.81 mmol), and potassium carbonate (0.216 g, 1.56 mmol) were dissolved in DMA (5 mL). The reaction mixture was stirred at r.t for 16 h. 2-Iodopropane (0.154 g, 0.91 mmol) was added to the solution and stirring continued for an additional 8 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated $NaHCO_3$ (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford isopropyl 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinate as a solid, which was used crude.

(c) Isopropyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate bis(trifluoroacetate)

Isopropyl 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinate (0.376 g, 1.00 mmol) was dissolved in DCM (1 mL). TFA (1.16 mL, 15.1 mmol) was added slowly. The reaction mixture was stirred at r.t for 16 h. The mixture was concentrated under reduced pressure to afford isopropyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate bis(trifluoroacetate) as a solid, which was used crude assuming a 100% conversion.

(d) 6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid isopropyl ester

1,1'-carbonylbis(1H-imidazole) (0.035 g, 0.216 mmol) and 1-phenylmethanesulfonamide (0.037 g, 0.216 mmol) were dissolved in DCE (2 mL) and stirred for 16 h at r.t. Isopropyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate bis(trifluoroacetate) (0.102 g, 0.216 mmol) in DCE (2 mL) and DIPEA (0.564 mL, 0.740 mmol) were added to the reaction mixture and stirring continued at r.t for 16 h. The reaction mixture was heated at 70 °C for 16 h. 1,1'-carbonylbis(1H-imidazole) (0.035 g, 0.216 mmol) and 1-phenylmethanesulfonamide (0.037 g, 0.216 mmol) were added to the solution and the reaction mixture was heated at 70

°C for 16 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (40 mL). The combined organics were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Trituration (1:1 EtOAc/hexanes) gave 6-[3-({[(benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid isopropyl ester as a solid. Yield: 0.017 g (16.2 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (6H, d, J = 6.2 Hz), 2.62 (3H, s), 4.18 (2H, m), 4.55 (3H, m), 4.69 (2H, m), 5.03-5.09 (1H, m), 7.10 (1H, s), 7.32-7.40 (5H, m), 8.31 (1H, s), 10.5 (s, 1H).

MS $^m/_z$: 472 (M+1).

Example 27

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid tert-butyl ester

(a) *tert*-Butyl 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid

6-{3-[(*tert*-Butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid (0.400 g, 1.20 mmol), and *tert*-butyl imidocarbamate (0.964 g, 4.80 mmol) were dissolved in THF (5 mL) and heated at 80 °C for 27 h. The reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with DCM (40 mL) and filtered through a silica plug with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude product. Flash chromatography (1:6 EtOAc/hexanes) gave *tert*-butyl 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid as a solid. Yield: 0.342 g (73.2 %).

(b) *tert*-Butyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate dihydrochloride

tert-Butyl 6-{3-[(*tert*-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinic acid (0.342 g. 0.880 mmol) was dissolved HCl (1 M in dioxane, 4.40 mL, 4.40 mmol). The reaction mixture was stirred at r.t for 16 h and concentrated under reduced pressure to yield *tert*-butyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate dihydrochloride as a solid, which was used crude assuming 100 % conversion.

(c) **6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid tert-butyl ester**

1,1'-carbonylbis(1H-imidazole) (0.034 g, 0.208 mmol) and 1-phenylmethanesulfonamide (0.034 g, 0.208 mmol) were dissolved in DCE (2 mL) and stirred for 16 h at r.t. *tert*-Butyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate dihydrochloride (0.130 g, 0.208 mmol) in DCE (2 mL) and DIPEA (2.08 mL, 0.362 mmol) were added to this solution and stirred at r.t for 48 h. The reaction mixture was heated to 70 °C for 16 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (40 mL). The combined organics were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (1:6 EtOAc/hexanes) followed by trituration (1:1 EtOAc/hexanes) gave 6-[3-({[(benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid tert-butyl ester as a solid. Yield: 0.031 g (30 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.52 (9H, s), 2.60 (3H, s), 4.16 (2H, m), 4.55 (3H, m), 4.69 (2H, m), 7.10 (1H, s), 7.33-7.40 (5H, m), 8.23 (1H, s), 10.5 (1H, s).

MS $^m/_z$: 486 (M+1).

Example 28

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotic acid ethyl ester

(a) Ethyl 6-{3-[(tert-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinate

Ethyl 6-chloro-5-cyano-2-methylnicotinate (6.20 g, 29.4 mmol), tert-butyl azetidin-3-ylcarbamate (5.07 g, 29.4 mmol), and DIPEA (5.13 mL, 29.4 mmol) were dissolved in DCE (40 mL) and stirred at r.t for 1 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (40 mL). The combined organics were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (1:6 EtOAc/hexanes) gave ethyl 6-{3-[(tert-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinate as a solid. Yield: 7.00 g (66.0 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.2 Hz), 1.46 (9H, s), 2.70 (1H, s), 4.18-4.22 (2H, m), 4.30 (2H, q, J = 7.2 Hz), 4.59 (1H, s), 4.67-4.72 (2H, m), 5.00 (1H, s), 8.26 (1H, s).

MS $^m/_z$: 361 (M+1).

(b) Ethyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate bis(trifluoroacetate)

Ethyl 6-{3-[(tert-butoxycarbonyl)amino]azetidin-1-yl}-5-cyano-2-methylnicotinate (1.00 g, 2.77 mmol) was dissolved in DCM (10 mL). TFA (6.40 mL, 83.2 mmol) was added slowly. The reaction mixture was stirred at r.t for 30 minutes. The mixture was concentrated under reduced pressure to afford ethyl 6-(3-aminoazetidin-1-yl)-5-cyano-2-methylnicotinate bis(trifluoroacetate) as a solid, which was used crude assuming a 100% conversion.

(c) 6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotic acid ethyl ester

1,1'-carbonylbis(1H-imidazole) (0.054 g, 0.333 mmol) and 1-phenylmethanesulfonamide (0.057 g, 0.333 mmol) were dissolved in DCE (2 mL) and stirred for 16 h at r.t. 6-(3-Aminoazetidin-1-yl)-5-cyano-2-methylnicotinate bis(trifluoroacetate) (0.210 g, 0.333 mmol) in DCE (2 mL) and DIPEA (0.580 mL, 3.33 mmol) were added to this solution and stirred at r.t for 2 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (40 mL). The combined organics were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Trituration (1:1 EtOAc/hexanes) gave 6-[3-({[(benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotic acid ethyl ester as a solid. Yield: 0.073 g (47.9 %)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 2.63 (3H, s), 2.70 (1H, s), 4.18-4.19 (2H, m), 4.24 (2H, q, J = 7.1 Hz), 4.56 (3H, m), 4.70 (2H, m), 7.1 (1H, s), 7.32-7.43 (5H, m), 8.31 (1H, s).

MS $^m/_z$: 458 (M+1).

Example 29

6-(3-{2-[(Benzylsulfonyl)amino]-2-oxoethyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

(a) Piperidin-3-ylacetic acid potassium salt

Potassium trimethylsilanoate (0.89 g, 5.2 mmol) and ethyl piperidin-3-ylacetate (0.87 g, 6.8 mmol) were stirred in DCM (50 mL) at r.t for 2 days. Concentration of the reaction mixture

afforded solid piperidin-3-ylacetic acid as the potassium salt, which was used crude assuming complete conversion. Yield: 0.74 g (100 %).

(b) {1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperdin-3-yl}acetic acid

Ethyl 6-chloro-5-cyano-2-methylnicotinate (1.00 g, 4.45 mmol), piperidin-3-ylacetic acid (0.701 g, 4.90 mmol) and DIPEA (2.33 mL, 13.4 mmol) were dissolved in DMF (30 mL) and stirred at r.t for 3 days. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated NH_4Cl (2 x 25 mL), saturated $NaHCO_3$ (2 x 25 mL), brine (25 m), dried ($MgSO_4$) and concentrated under reduced pressure to afford crude material. Flash chromatography (9:1 EtOAc/hexanes with 1% HOAc) gave {1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperdin-3-yl}acetic acid as a solid. Yield: 0.791 g (54 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.39-1.44 (1H, m), 1.63-1.73 (1H, m), 1.78-1.85 (1H, m), 1.98-2.03 (1H, m), 2.16-2.24 (1H, m), 2.29-2.34 (1H, m), 2.40-2.46 (1H, m), 2.71 (3H, s), 3.08-3.13 (1H, m), 3.26-3.32 (1H, m), 4.31 (2H, q, J = 7.1 Hz), 4.44-4.50 (1H, m), 4.52-4.56 (1H, m), 8.33 (1H, s).

MS $^m/_z$: 330 (M-1).

(c) 6-(3-{2-[(Benzylsulfonyl)amino]-2-oxoethyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

{1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperdin-3-yl}acetic acid (0.152 g, 0.459 mmol), EDCI (0.114 g, 0.596 mmol), HOBt (0.081 g, 0.596 mmol), 1-phenylmethanesulfonamide (0.102 g, 0.596 mmol) and DIPEA (0.160 mL, 917 mmol) were dissolved in DCM (6 mL) and stirred at r.t for 18 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NH_4Cl (2 x 40 mL) and brine (40 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Flash chromatography (1:4 EtOAc/hexanes, 1.0 % AcOH gave 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester as a solid. Yield: 0.065 g (28 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35-1.40 (3H, m), 1.53-1.58 (1H, m), 1.64-1.71 (1H, m), 1.73-1.80 (1H, m), 1.93-2.00 (1H, m), 2.11-2.22 (2H, m), 2.27-2.34 (1H, m), 2.68 (3H, s), 3.09-3.16 (1H, m), 3.30-3.38 (1H, m), 4.29-4.40 (4H, m), 4.68 (2H, s), 7.37-7.38 (5H, m), 7.70 (1H, br s), 8.33 (1H, s).

MS $^m/_z$: 485 (M+1).

Example 30

6-(4-{[(Benzylsulfonyl)amino]carbonyl}-4-methylpiperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

(a) 1-*tert*-Butyl 4-methyl piperidine-1,4-dicarboxylate

1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid (3.00 g, 13 mmol) was dissolved in MeOH (50 mL) and $TMSCHN_2$ (32.7 mL of a 2 M solution in hexanes, 65 mmol) was added drop-wise at r.t. $TMSCHN_2$ was added until a persistent yellow color was produced indicating excess reagent. AcOH was added drop-wise to quench the excess $TMSCHN_2$ and the the reaction mixture was concentrated under reduced pressure and azeotroped with Toluene (3 × 30 mL) to remove any trace MeOH or AcOH. The crude 1-*tert*-Butyl 4-methyl piperidine-1,4-dicarboxylate was used without further purification.

(b) 1-*tert*-Butyl 4-methyl 4-methylpiperidine-1,4-dicarboxylate

DIPA (2.40 mL, 17 mmol) was dissolved in THF (60 mL) and cooled to 0 °C. Butyl lithium 1.6 M in Hexanes (9.81 mL, 16 mmol) was added drop-wise and the system stirred at 0 °C for 1h. The reaction mixture was cooled to -78 °C and a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (3.18 g, 13 mmol) in THF (30 mL) was added drop-wise over 30 minutes. The reaction mixture was stirred at -78 °C for 2 h and then Iodomethane (1.31 mL, 21 mmol) in THF (10 mL) was added in one portion and the reaction mixture stirred for 2 h. The system was allowed to warm to r.t overnight. The reaction mixture was quenched with saturated NH_4Cl (100 mL) and extracted into EtOAc (100 mL). The combined organics were washed with brine (70 mL) and dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude 1-*tert*-butyl 4-methyl 4-methylpiperidine-1,4-dicarboxylate as a solid, which was used without further purification.

(c) Methyl 4-methylpiperidine-4-carboxylate

1-*tert*-Butyl 4-methyl 4-methylpiperidine-1,4-dicarboxylate (3.37 g, 13.1 mmol) was suspended in THF (15 mL) and 4 M HCl in 1,4-dioxane (65.4 mL, 262 mmol) was added and the reaction mixture stirred at r.t until complete consumption of the starting material was observed by TLC analysis. The reaction mixture was concentrated under reduced pressure to afford the crude material. The solids were partitioned between saturated $NaHCO_3$ and DCM.

The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography, (eluant 0.5 % TEA, 2 % MeOH / DCM - 1 % TEA, 5 % MeOH / DCM) gave methyl 4-methylpiperidine-4-carboxylate as an oil. Yield: 0.910 g (44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, s), 1.44-1.55 (2H, m), 2.09-2.20 (2H, m), 2.69-2.80 (2H, m), 2.98-3.08 (2H, m), 3.72 (3H, s), 3.99 (1H, br s).

MS $^m/_z$: 158 (M+1).

(d) 4-Methylpiperidine-4-carboxylic acid hydrochloride

Methyl 4-methylpiperidine-4-carboxylate (0.300 g, 1.9 mmol) was suspended in THF (30 mL) and potassium trimethylsilanolate (2.4 g, 19 mmol) was added. The system was heated at reflux overnight and then cooled to r.t. 4 M HCl in 1,4-dioxane (12 mL, 48 mmol) was added and the system concentrated under reduced pressure to afford crude 4-methylpiperidine-4-carboxylic acid hydrochloride as a solid, which was used without further purification.

(e) 1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]-4-methylpiperidine-4-carboxylic acid

Ethyl 6-chloro-5-cyano-2-methylnicotinate (0.28 g, 1.3 mmol) and 4-methylpiperidine-4-carboxylic acid hydrochloride (0.34 g, 1.9 mmol) were suspended in DMF (20 mL) and DIPEA (1.1 mL, 6.3 mmol) was added. The reaction mixture was stirred at r.t until complete consumption of the starting materieal was observed by HPLC analysis. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (70 mL), water (2 × 70 mL) and brine (50 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude material. Flash column chromatography (1:3 EtOAc/hexanes, 0.5 % AcOH to 1:2 EtOAc/hexanes, 0.5 % AcOH) gave 1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]-4-methylpiperidine-4-carboxylic acid as a solid. Yield: 0.179 g (43%).

^{1}H NMR (400 MHz, DMSO- d_6): δ 1.20 (3H, s), 1.30 (3H, t, J = 7.1Hz), 1.44-1.54 (2H, m), 2.02-2.11 (2H, m), 2.63 (3H, s), 3.39-3.48 (2H, m), 4.15-4.29 (4H, m), 8.32 (1H, s), 12.52 (1H, br s).

MS $^m/_z$: 332 (M+1).

(f) 6-(4-{[(Benzylsulfonyl)amino]carbonyl}-4-methylpiperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]-4-methylpiperidine-4-carboxylic acid (0.074 g, 0.22 mmol), EDCI (0.056 g, 0.29 mmol) and HOBt (0.039 g, 0.29 mmol) were dissolved in DCM (10 mL) at r.t. The reaction mixture was stirred at r.t for 30 minutes and then 1-phenylmethane sulfonamide (0.054 g, 0.31 mmol) and DIPEA (0.23 mL, 1.3 mmol) were added. The reaction mixture was stirred at r.t until complete consumption of starting material was observed by HPLC analysis. The reaction mixture was diluted with DCM (20 mL) and washed with saturated NH_4Cl (20 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (3:7 EtOAc/hexanes, 0.5 % AcOH to 1:1 EtOAc/hexanes, 0.5 % AcOH) followed by preparative HPLC gave 6-(4-{[(benzylsulfonyl)amino]carbonyl}-4-methylpiperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester as a solid. Yield: 0.038 g (35 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, s), 1.38 (3H, t, J = 7.0 Hz), 1.54-1.62 (2H, m), 2.00-2.09 (2H, m), 2.73 (3H, s), 3.52-3.62 (2H, m), 4.07-4.17 (2H, m), 4.33 (2H, q, J = 7.0 Hz), 4.72 (2H, s), 7.26-7.27 (2H m), 7.37-7.39 (3H, m), 7.47 (1H s), 8.35 (1H, s).

MS $^m/_z$: 485 (M+1).

Example 31

N-(Benzylsulfonyl)-1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxamide

(a) *tert*-Butyl 4-{[(benzylsulfonyl)amino]carbonyl}piperidine-1-carboxylate

Triethylamine (591 g, 5840 mmol) was added to a stirred suspension of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (448 g, 1954 mmol), LiCl (23.1 g, 545 mmol) and TBTU (657 g, 2046 mmol) in THF (3000 mL) under an atmosphere of nitrogen at r.t.. A solution of 1-phenylmethanesulfonamide (352 g in 1300 mL THF, 2056 mmol) was added after 1.5 hours and the stirring was continued over night . The solvent was removed in vaccuo to give a thick grey-beige slurry (volume about 2500 mL). EtOAc (3500 mL) was added followed by an aqueous solution of HCl (1960 mL 3.6 M HCl and 1960 mL water). The water phase was removed and the organic phase was washed with 2 x 1500 mL 1 M HCl. The organic phase was cooled to 0°C which gave a precipitate of HOBt that was filtered off. Most of the solvent was removed in vaccuo to give a thick grey-white slurry. EtOH (50 %, 4000 mL) was added and the slurry was stirred for 1.5 hours. The precipitated product was filtered off , washed with 50 % EtOH (500 mL + 2 x 1500 mL) and dried in a vaccum oven at 25 oC

to give tert-butyl 4-[(benzylsulfonyl)carbamoyl]piperidine-1-carboxylate as a white solid. Yield 584 g (78 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.54-1.61 (2H, m), 1.70-1.74 (2H, m), 2.19-2.27 (1H, m), 2.68-2.75 (2H, m), 4.07-4.12 (2H, m), 4.66 (2H, s), 7.32-7.41 (5H, m), 7.54 (1H, br s).

(b) N-(benzylsulfonyl)piperidine-4-carboxamide

tert-Butyl 4-[(benzylsulfonyl)carbamoyl]piperidine-1-carboxylate (583 g, 1524 mmol) was suspended in formic acid (3000 mL) under a nitrogen atmosphere and the reaction was stirred for 20 minutes. The reaction was foaming due to the gas evolution and formic acid (500 mL) was used to wash down the foam from the reaction vessel walls. After 2 hours the foaming had stopped and the reaction was clear with a few solids left. The reaction was stirred over night and 2500 ml of formic acid was removed in vaccuo. Water (1000 mL) was added and the reaction was filtered. The clear solution was evaporated and water (3000 mL) was added. A saturated ammonium hydroxide solution in water was used (totally 390 mL was added and the pH was going from 3.10 to 6.10) to neutralize the acidic solution and at the endpoint (pH=6.10) a heavy precipitate of the product was formed. The mixture was stirred over night and the precipitate was filtered off and washed with water (1000 mL). Drying in a vaccum oven at 25oC gave N-(benzylsulfonyl)piperidine-4-carboxamide as a white powder. Yield 372.4 g (87%).

^{1}H NMR (400 MHz, DMSO- d_6): δ 1.60-1.72 (2H, m), 1.75-1.84 (2H, m), 2.10-2.19 (1H, m), 2.77-2.87 (2H, m), 3.10-3.18 (2H, m), 4.23 (2H, s), 7.18-7.28 (5H, m), 8.17 (1H, br s).

(c) *N*-(Benzylsulfonyl)-1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxamide

A suspension of 2,3-dichloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridine (0.300 g, 1.23 mmol), N-(benzylsulfonyl)piperidine-4-carboxamide (0.367 g, 1.30 mmol) and DIPEA (0.645 mL, 3.70 mmol) in DMA (10 mL) was stirred at 80°C for 24 h. The reaction mixture was cooled to r.t and poured into EtOAc (60 mL) and saturated. NH_4Cl (30 mL). The organics were washed with water (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude material. Flash chromatography (3:7 EtOAc / hexanes with 0.5 % AcOH) furnished *N*-(Benzylsulfonyl)-1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxamide as a solid. Yield: 0.297 g (49 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, t, J = 7.0 Hz), 1.86-1.91 (4H, m), 2.29-2.38 (1H, m), 2.75 (2H, q, J = 7.0 Hz), 2.84-2.91 (2H, m), 3.97-4.02 (2H, m), 4.69 (2H, s), 6.82 (1H, s), 7.35-7.41 (5H, m), 7.47 (1H, br s), 8.15 (1H, d, J = 2.0 Hz), 8.74 (1H, d, J = 2.0 Hz).
MS $^m/_z$: 489 (M+1).

Example 32

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid cyclopentyl ester

(a) Sodium cylopentanolate

Cyclopentyl alcohol (5 mL) was cooled to 0 °C. Sodium hydride (95%, 0.018 g, 0.713 mmol) was slowly added. The solution was used crude assuming a 100% conversion.

(b) 6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid cyclopentyl ester

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester (0.070 g, 0.158 mmol, see Example 46) and molecular sieves (4 Angstrom, 0.070 g) were suspended in cyclopentanol (5 mL) and DMSO (2 mL) and stirred at r.t for 10 minutes. Sodium cylopentanolate (0.286 g, 3.48 mmol) in cyclopentyl alcohol (5 mL) was added and the solution was stirred for 10 minutes. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The reaction mixture was filtered and then concentrated under reduced pressure. Water (10 mL) was added to the solution and the combined aqueous was washed with EtOAc (3 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (30% EtOAc with 0.5% AcOH) gave 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid cyclopentyl ester as a solid. Yield: 0.031 g (41 %).
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.56-1.64 (2H, m), 1.69-1.80 (4H, m), 1.84-1.95 (2H, m), 2.63 (3H, m) 3.52-3.60 (1H, m), 4.26-4.35 (2H, m), 4.37-4.45 (2H, m), 4.76 (2H, s) 5.22-5.30 (1H, m), 7.31-7.43 (5H, m) 8.29 (1H, s), 11.8 (1H, s).
MS $^m/_z$: 483 (M+1).

Example 33

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid propyl ester

To a solution of 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester (0.078 g, 0.17 mmol, See Example 42) in THF (15 mL) and n-Propanol (15 mL) were added 4 Angstrom molecular sieves (0.5 g). The reaction mixture was stirred for 1 h and then cooled to 0°C. After the addition of NaH (60% dispersion in mineral oil, 0.013 g, 0.33 mmol), the mixture was warmed to r.t and stirred for 2 h. Addition of acetic acid (5.0 mL), filtration through celite, concentration followed by azeotroping with toluene (2 x 50 mL) provided the crude material. Trituration with MeOH (1 x 25 mL) and then EtOAc (1 x 25 mL) furnished 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid propyl ester as a solid. Yield: 0.027 g (34 %).

^{1}H NMR (400 MHz, DMSO- d_6): δ 0.96 (3H, t, J = 7.5 Hz), 1.59-1.66 (2H, m), 1.67-1.76 (2H, m), 1.82-1.86 (2H, m), 2.55-2.62 (1H, m), 2.65 (3H, s), 3.11-3.17 (2H, m), 4.17 (2H, t, J = 6.7 Hz), 4.56-4.52 (2H, m), 4.70 (2H, s), 7.28-7.31 (2H, m), 7.38-7.43 (3H, m), 8.34 (1H, s), 11.61 (1H, br s).

MS $^m/_z$: 485 (M+1).

Example 34

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-isopropylnicotinic acid ethyl ester

(a) Ethyl 2-((dimethylamino)methylene)-4-methyl-3-oxopentanoate

1,1-Dimethoxy-N,N-dimethylmethanamine (4.96 mL, 37.2 mmol) was added drop-wise to ethyl 4-methyl-3-oxopentanoate (5.00 mL, 31.0 mmol) while stirring at r.t. The reaction mixture was allowed to stir at r.t for 18 h and was then concentrated under reduced pressure and azeotroped with toluene (2 x 20 mL) producing ethyl 2-((dimethylamino)methylene)-4-methyl-3-oxopentanoate

as an oil which was used without purification. Yield: 6.61 g (100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (6H, d, J = 6.9 Hz), 1.31 (3H, t, J = 7.3 Hz), 3.00 (6H, br s), 3.26 (1H, br s), 4.21 (2H, q, J = 7.3 Hz), 7.60 (1H, s).

(b) Ethyl 5-cyano-2-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxylate

To a suspension of 2-cyanoacetamide (2.74 g, 32.6 mmol) in THF (100 mL) was added NaH (60% dispersion in mineral oil, 1.36 g, 34.1 mmol) added. The system was stirred at r.t until gas evolution ceased, at which point ethyl 2-((dimethylamino)methylene)-4-methyl-3-

oxopentanoate (6.61 g, 31.0 mmol) was added in one portion. The reaction mixture was stirred at r.t for 18 h and concentrated under reduced pressure to afford crude intermediate. The solids were dissolved in a minimum amount of warm water and then acidified to pH 1 with 5 N HCl. Filtration followed by drying under vacuum produced ethyl 5-cyano-2-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxylate. Yield: 6.46 g (89 %).

^{1}H NMR (400 MHz, DMSO- d_6): δ 1.25 (6H, d, J = 7.1 Hz), 1.29 (3H, t, J = 7.3 Hz), 4.01-4.12 (1H, m), 4.23 (2H, q, J = 7.3 Hz), 8.43 (1H, s), 12.56 (1H, br s).

MS $^m/_z$: 235 (M+1).

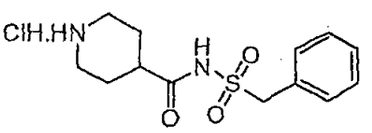
(c) Ethyl 6-chloro-5-cyano-2-isopropylnicotinate

A suspension of ethyl 5-cyano-2-isopropyl-6-oxo-1,6-dihydropyridine-3-carboxylate (6.46 g, 27.6 mmol) in $POCl_3$ (10.1 mL, 110 mmol) was heated at 100°C for 6 h. The reaction mixture was poured onto ice and then basified with solid K_2CO_3. The aqueous phase was extracted with DCM (3 x 100 mL) and the organics was dried ($MgSO_4$) and concentrated under reduced pressure to afford ethyl 6-chloro-5-cyano-2-ispropylnicotinate, which was used without further purification. Yield: 6.54 g (93 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (6H, d, J = 6.8 Hz), 1.42 (3H, t, J = 7.2 Hz), 3.88-3.98 (1H, m), 4.41 (2H, q, J = 7.2 Hz), 8.37 (1H, s).

MS $^m/_z$: 254 (M+1).

(d) *N*-(Benylsulfonyl)piperidine-4-carboxamide hydrochloride



To a suspension of *tert*-butyl 4-{[(benzylsulfonyl)amino]carbonyl}piperidine-1-carboxylate (4.18 g, 10.9 mmol) in THF (100 mL) was added 4 M HCl in dioxane (54.6 mL, 218 mmol) and the reaction mixture was stirred at r.t for 18 h. The solids were collected by filtration and washed with EtOAc (100 mL) and then placed under vacuum to yield *N*-(benylsulfonyl)piperidine-4-carboxamide hydrochloride as a solid. Yield: 2.50 g (72 %).

^{1}H NMR (400 MHz, DMSO- d_6): δ 1.70-1.78 (2H, m), 1.83-1.88 (2H, m), 2.47-2.53 (1H, m), 2.80-2.89 (2H, m), 3.26-3.31 (2H, m), 4.71 (2H, s), 7.27-7.30 (2H, m), 7.39-7.41 (3H, m), 8.53 (1H, br s), 8.79 (1H, br s), 11.70 (1H, br s).

(e) 6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-isopropylnicotinic acid ethyl ester

A mixture of ethyl 6-chloro-5-cyano-2-isopropylnicotinate (0.184 g, 0.728 mmol), N-(benylsulfonyl)piperidine-4-carboxamide hydrochloride (0.232 g, 0.728 mmol) and DIPEA (0.380 mL, 2.18 mmol) in DMF (3.0 mL) was heated to 60°C for 5 h. The reaction mixture was diluted with EtOAc (30 mL), washed with saturated NH_4Cl (2 x 15 mL) and brine (15 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Flash chromatography (DCM followed by 1 % MeOH, 1 % HOAc in DCM) produced a solid, which was triturated with 1:1 Et_2O/hexanes (25 mL) to afford 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-isopropylnicotinic acid ethyl ester as a solid. Yield: 0.300 g (81 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (6H, d, J = 6.5 Hz), 1.38 (3H, t, J = 7.3 Hz), 1.74-1.90 (4H, m), 2.41-2.48 (1H, m), 3.11-3.18 (2H, m), 3.95-4.05 (1H, m), 4.32 (2H, q, J = 7.3 Hz), 4.64-4.69 (4H, m), 7.31-7.33 (2H, m), 7.37-7.43 (3H, m), 8.10 (1H, br s), 8.31 (1H, s).

MS $^m/_z$: 499 (M+1).

Example 35

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-ethylnicotinic acid ethyl ester

(a) Ethyl 2-((dimethylamino)methylene)-3-oxopentanoate

1,1-Dimethoxy-N,N-dimethylmethanamine (5.09 mL, 42.0 mmol) was added drop-wise to ethyl 3-oxopentanoate (5.0 mL, 35.0 mmol) while stirring at r.t. The reaction mixture was stirred at r.t for 18 h and then was concentrated under reduced pressure and azeotroped with toluene (2 x 20 mL) producing ethyl 2-((dimethylamino)methylene)-3-oxopentanoate as an oil which was used without purification. Yield: 6.98 g (100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, t, J = 7.7 Hz), 1.32 (3H, t, J = 7.7 Hz), 2.67-2.69 (2H, m), 3.01 (6H, br s), 4.22 (2H, q, J = 7.2 Hz), 7.64 (1H, s).

(b) Ethyl 5-cyano-2-ethyl-6-oxo-1,6-dihydropyridine-3-carboxylate

To a suspension of 2-cyanoacetamide (3.09 g, 36.8 mmol) in THF (100 mL) was added NaH (60 % dispersion in mineral oil, 1.54 g, 38.5 mmol) added. The mixture was stirred at r.t until gas evolution ceased, at which point ethyl 2-((dimethylamino)methylene)-3-oxopentanoate

(6.98 g, 35.0 mmol) was added in one portion. The reaction mixture was stirred at r.t for 18 h and concentrated under reduced pressure to afford crude intermediate. The solids were dissolved in a minimum amount of warm water and then acidified to pH 1 with 5 M HCl. Filtration followed by drying under vacuum produced ethyl 5-cyano-2-ethyl-6-oxo-1,6-dihydropyridine-3-carboxylate as a solid. Yield: 6.28 g (81 %).

^{1}H NMR (400 MHz, DMSO- d_6): δ 1.18 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.0 Hz), 2.95 (2H, q, J = 7.3 Hz), 4.24 (2H, q, J = 7.0 Hz), 8.45 (1H, s), 12.79 (1H, br s).

MS $^m/_z$: 221 (M+1).

(c) Ethyl 6-chloro-5-cyano-2-ethylnicotinate

A suspension of ethyl 5-cyano-2-ethyl-6-oxo-1,6-dihydropyridine-3-carboxylate (6.28 g, 28.5 mmol) in $POCl_3$ (10.4 mL, 114 mmol) was heated to 100°C for 6 h. The reaction mixture was poured onto ice and then basified with solid K_2CO_3. The aqueous phase was extracted with DCM (3x 100 mL) and the organics dried ($MgSO_4$) and concentrated under reduced pressure to afford ethyl 6-chloro-5-cyano-2-ethylnicotinate as a solid, which was used without further purification. Yield: 6.17 g (91 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, t, J = 7.4 Hz), 1.42 (3H, t, J = 7.4 Hz), 3.23 (2H, q, J = 7.4 Hz), 4.42 (2H, q, J = 7.4 Hz), 8.45 (1H, s).

MS $^m/_z$: 239 (M+1).

(d) 6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-ethylnicotinic acid ethyl ester

A solution of ethyl 6-chloro-5-cyano-2-ethylnicotinate (0.143 g, 0.599 mmol), N-(benylsulfonyl)piperidine-4-carboxamide hydrochloride (0.191 g, 0.599 mmol, See example 34(d)) and DIPEA (0.131 mL, 1.80 mmol) in DMF (3.0 mL) was heated to 60°C for 5 h. The reaction mixture was diluted with EtOAc (30 mL), washed with saturated NH_4Cl (2 x 15 mL) and brine (15 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Flash chromatography (DCM followed by 1 % MeOH, 1 % HOAc in DCM) produced a solid, which was triturated with 1:1 Et_2O/hexanes (25 mL) to afford 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-ethylnicotinic acid ethyl ester as a solid. Yield: 0.250 g (84 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.4 Hz), 1.38 (3H, t, J = 7.0 Hz), 1.74-1.82 (2H, m), 1.84-1.90 (2H, m), 2.39-2.47 (1H, m), 3.10-3.18 (4H, m), 4.32 (2H, q, J = 7.0 Hz), 4.66-4.70 (4H, m), 7.32-7.35 (2H, m), 7.38-7.42 (3H, m), 7.70 (1H, br s), 8.35 (1H, s).
MS $^m/_z$: 485 (M+1).

Example 36

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid 2,2-dimethylpropyl ester

(a) 1-{3-cyano-5-[(2,2-dimethylpropoxy)carbonyl]-6-methylpyridin-2-yl}azetidine-3-carboxylic acid

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid (0.218 g, 0.92 mmol) was suspended in THF (20 mL) and DMSO (4 mL) and sodium 2,2-dimethylpropan-1-olate (3.684 mL, 3.684 mmol) added. The reaction mixture was stirred at r.t until complete conversion of the starting material to product was observed by HPLC analysis. The reaction was stopped with 1 N HCl (10 mL) and the reaction mixture diluted with water (50 mL) and extraced into EtOAc (2 × 40 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude material. Flash chromatography (3:7 EtOAc/hexanes, 0.5 % AcOH to 1:1 EtOAc/hexanes, 0.5 % AcOH) gave 1-{3-cyano-5-[(2,2-dimethylpropoxy)carbonyl]-6-methylpyridin-2-yl}azetidine-3-carboxylic acid as a solid. Yield: 0.167 g (55 %).

(b) 6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid 2,2-dimethylpropyl ester

1-{3-Cyano-5-[(2,2-dimethylpropoxy)carbonyl]-6-methylpyridin-2-yl}azetidine-3-carboxylic acid (0.080 g, 0.24 mmol), EDCI (0.060 g, 0.31 mmol) and HOBt (0.042 g, 0.31 mmol) were dissolved in DCM (5 mL) at r.t. The reaction mixture was stirred at r.t for 30 minutes and then phenylmethanesulfonamide (0.058 g, 0.34 mmol) and DIPEA (0.25 mL, 1.45 mmol) were added. The reaction mixture was stirred at r.t until complete consumption of starting material was observed by HPLC analysis. The reaction mixture was diluted with DCM (20 mL) and washed with saturated NH_4Cl (20 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (3:7 EtOAc/hexanes, 0.5 % AcOH to 1:1 EtOAc/hexanes, 0.5 % AcOH) followed by

preparative HPLC gave 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid 2,2-dimethylpropyl ester as a solid. Yield: 0.016 g (14 %).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (9H, s), 2.74 (3H, s), 3.26-3.56 (1H, m), 3.97 (2H, s), 4.43-4.50 (4H, m), 4.69 (2H, s), 7.36-7.56 (5H, m), 8.27 (1H, s).
MS $^m/_z$: 485 (M+1).

Example 37

***N*-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide**

(a) Ethyl 5-cyano-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,6-dihydropyridine-3-carboxylate

The sodium salt of ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (8.81 g, 38.6 mmol) was distributed equally into 8 Smith process vials. To each vial was added DCM (3 mL), [2-(chloromethoxy)ethyl](trimethyl)silane (1.78 g,10.7 mmol), and then DIPEA (2.07 g, 16.0 mmol). Each vial was heated in a microwave oven, single node heating, at 120 °C for 10 minutes. Extra [2-(chloromethoxy)ethyl] (trimethyl)silane (0.445 g, 2.68 mmol) was added to each vial and the single node heating was continued at 120 °C for 10 minutes. The reaction mixtures were combined and vacuum filtered. Purification by flash chromatography on SiO_2 with heptane/EtOAc 4:1 or 3:1 afforded the pure product. Yield: 8.376 g (58 %).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 5.46 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.52 (t, J = 8.0 Hz, 2H), 2.78 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.75 (t, J = 8.0 Hz, 2H), -0.18 (s, 9 H).
MS $^m/_z$: 335 (M-1).

(b) 5-Cyano-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,6-dihydropyridine-3-carboxylic acid

Ethyl 5-cyano-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,6-dihydropyridine-3-carboxylate (8.371 g, 24.9 mmol) was dissolved in THF (50 mL) and 1M LiOH (100 mL) was added. The reaction mixture was stirred at rt for 3h. The conversion was complete according to LC/MS. 4M HCl was added to pH 2-3. The WATER phase was extracted with EtOAc (3x100 mL). The organic phases were combined and dried with sodium sulphate and evaporated. To give a crude material.Yield: 8.35 g (109 %). The isomeric ethyl 5-cyano-2-methyl-6-{[2-(trimethylsilyl)ethoxy] methoxy}nicotinate was formed as the main product

according to LC/MS, which showed a product/by-product ratio of 25:75. No attempt was made to separate the isomers.

MS $^{m}/_{z}$: 307 (M-1).

(c) 5-Cyano-*N*-(2-hydroxybutyl)-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,6-dihydropyridine-3-carboxamide

A mixture (7.67 g, 24.9 mmol) of 5-cyano-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl} -1,6-dihydropyridine-3-carboxylic acid and the isomer ethyl 5-cyano-2-methyl-6-{[2-(trimethylsilyl)ethoxy] methoxy}nicotinate, in a ratio of 25:75 according to LC/MS, was dissolved in DCM (125 mL). EDCI (6.2 g, 27.4 mmol) and HOBt (5.04 g, 37.3 mmol) were added and the reaction mixture was stirred at rt for 40 minutes. 1-aminopropan-2-ol (2.44 g, 27.7 mmol) in DIPEA (16.1 g, 124.4 mmol) was added and stirring at rt was continued for 1.5h. According to LC/MS only the minor isomer had been converted at this point. Stirring at rt was continued for 16h further without any change in LC/MS. The organic phase was extracted with 10% potassium carbonate (2x125 mL), brine (2x125 mL), dried with sodium sulphate and evaporated. This gave 12.21 g crude product. Purification by flash chromatography on Si-gel with heptane/EtOAc fractions, first 1:2, then 1:4, eluted afforded 5-cyano-*N*-(2-hydroxybutyl)-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl} -1,6-dihydropyridine-3-carboxamide.

Yield: 3.28 g (35 %). When all product had been eluted, elution was done with heptane/EtOAc 1:4 + 1% formic acid. In this way, 2.46 g of ethyl 5-cyano-2-methyl-6-{[2-(trimethylsilyl)ethoxy] methoxy}nicotinate was recovered.

^{1}H NMR (400 MHz, $CDCl_3$): δ -0.13 (s, 9H), 0.87-0.77 (m, 5H), 1.44-1.31 (m, 2H), 2.58 (s, 3H), 3.15-3.06 (m, 1H), 3.46-3.38 (m, 1H), 3.60-3.50 (m, 4H), 5.41 (s, 2H), 7.26-7.21 (m, 1H), 7.77 (s, 1H)

MS $^{m}/_{z}$: 378 (M-1).

(d) 5-Cyano-2-methyl-6-oxo-*N*-(2-oxobutyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,6-dihydropyridine-3-carboxamide

Oxalyl chloride (0.39 g, 3.05 mmol) was dissolved in DCM (2 mL) under an atmosphere of nitrogen and the solution was cooled to –78 °C. DMSO (0.37 g, 4.69 mmol) in DCM (1 mL) was added dropwise and the mixture was stirred at –78 °C for less than 5 minutes. 5-cyano-*N*-(2-hydroxybutyl)-2-methyl-6-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl} -1,6-

dihydropyridine-3-carboxamide (0.89 g, 2.35 mmol) in DCM (2 mL) was added during 2 minutes and stirring at –78 °C was continued for 1h. TEA (1.19 g, 11.7 mmol) was added. After stirring for 15 minutes the cooling bath removed and the reaction mixture was stirred at ambient temperature for 15 minutes. Water (10 mL) was added and the water phase was extracted with DCM (3x15 mL). The organic phases were combined and dried with sodium sulphate and evaporated to give the crude product which was used without further purification. Yield: 0.780 g (88 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.12 (s, 9H), 0.81 (t, J = 8.2 Hz, 2H), 0.97 (t, J = 7.4 Hz, 2H), 2.40 (q, J = 7.4 Hz, 2H), 2.63 (s, 3H), 3.55 (t, J = 8.2 Hz, 2H), 4.09 (d, J = 5.3 Hz, 2H), 5.45 (s, 2H), 7.50 (t, J = 5.3 Hz, 1H), 7.86 (s, 1H)

MS $^m/_z$: 376 (M-1).

(e) 5-(5-Ethyl-1,3-oxazol-2-yl)-6-methyl-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydropyridine-3-carbonitrile

5-cyano-2-methyl-6-oxo-*N*-(2-oxobutyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,6-dihydropyridine-3-carboxamide (2.761 g, 7.31 mmol) was dissolved in THF (9.6 mL) and the solution was transfered equally into 3 Smith process vials. To each vial was added (Methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (1.162 g, 4.88 mmol). The vials were sealed and heated in a microwave oven, single node heating, at 80 °C for 2 minutes. LC/MS on each vial showed complete conversion. The reaction mixtures were combined and evaporated to give 6.431 g of a crude material. Filtration through a Si-plug (10 g) with Heptane/EtOAc 1:1 (100 mL) afforded 5-(5-ethyl-1,3-oxazol-2-yl)-6-methyl-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydropyridine-3-carbonitrile. Yield: 1.766 g (67 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.20 (s, 9H), 0.74 (t, J = 8.0 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H), 2.55 (q, J = 7.5 Hz, 2H), 2.82 (s, 3H), 3.52 (t, J = 8.0 Hz, 2H), 5.46 (s, 2H), 6.62 (s, 1H), 8.09 (s, 1H)

MS $^m/_z$: 358 (M-1).

(f) 5-(5-Ethyl-1,3-oxazol-2-yl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile

A TFA/DCM mixture (1:1, 10 mL) was added to (5-(5-ethyl-1,3-oxazol-2-yl)-6-methyl-2-oxo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,2-dihydropyridine-3-carbonitrile (1.682 g, 4.68 mmol) and the reaction mixture was stirred at rt for 4h. According to LC/MS the reaction was complete. The reaction mixture was evaporated. DCM (10 mL) was added and the mixture

was dried with sodium sulphate and evaporated. This gave 0.263 g crude material. Purification by flash chromatography on Si-gel with DCM/MeOH (69:1, then 39:1) afforded the title compound. Yield: 0.263 g (82 %).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (br t, J = 7.5 Hz, 3H), 2.68 (s, 3H), 2.73 (br q, J = 7.5 Hz, 2H), 7.00 (br s, 1H), 8.51 (s, 1H), 12.97 (s, 1H)

MS $^m/_z$: 230 (M+1).

(g) 2-Chloro-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylnicotinonitrile

5-(5-ethyl-1,3-oxazol-2-yl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (0.069 g, 0.30 mmol) was dissolved in DCM (0.8 mL) in a Smith process vial and oxalyl chloride (0.573 g, 4.51 mmol) and then DMF (0.022 g, 0.3 mmol) were added at 0 °C. The reaction mixture was heated in the sealed vial on an oil bath at 50 °C for 2.5h. LC/MS showed 33 % wanted product and 45 % starting material. Stirring at the same temperature was continued. After 1.5h further, extra DMF (0.022 g, 0.30 mmol) was added. Stirring at the same temperature was performed for 7.5h further. LC/MS showed 64 % wanted product and 8 % starting material. The reaction mixture was evaporated and mixed with a batch that was prepared in the following manner:

5-(5-ethyl-1,3-oxazol-2-yl)-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (0.179 g, 0.78 mmol) was dissolved in DCM (2.4 mL) in a Smith process vial and oxalyl chloride (1.486 g, 11.70 mmol) and then DMF (0.057 g, 0.78 mmol) were added at 0 °C. The reaction mixture was heated in the sealed vial on an oil bath at 50 °C for 4h. LC/MS showed 40 % wanted product and 22 % starting material. Extra DMF (0.057 g, 0.78 mmol) was added. Stirring at the same temperature was performed for 16h further. LC/MS showed 35 % wanted product and no starting material. The material was evaporated. Purification of the combined batches was done by flash chromatography on Si-gel with DCM/MeOH 199:1 as eluent to afford 2-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylnicotinonitrile. Yield: 0.027g (10 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, J = 7.5 Hz, 3H), 2.80 (q, J = 7.5 Hz, 2H), 3.00 (s, 3H), 6.97 (s, 1H), 8.52 (s, 1H)

(h) 1-[3-Cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid

2-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylnicotinonitrile (0.056 g, 0.23 mmol) was dissolved in dry EtOH (4 mL) in a Smith process vial. Piperidine-3-carboxylic acid (0.051 g,

0.40 mmol) was added and the sealed vial was heated in a microwave oven, single node heating, at 120 °C for 20 minutes. LC/MS showed the reaction to be incomplete. TEA (0.233 g, 2.30 mmol) and extra Piperidine-3-carboxylic acid (0.015 g, 0.11 mmol) were added and the sealed vial was then heated in a microwave oven, single node heating, at 100 °C for 20 minutes. LC/MS showed the reaction to be complete. The reaction mixture was evaporated. 1M HCl (3 mL) was added and the mixture was extracted with DCM (3x3 mL) by using a phase separator. This gave the crude product which was used without further purification. Yield: 0.086 g (110%)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J = 7.5 Hz, 3H), 1.78-1.62 (m, 2H), 1.99-1.86 (m, 2H), 2.51-2.39 (m, 1H), 2.67-2.57 (m, 5H), 3.16-3.04 (m, 2H), 4.43-4.32 (m 2H), 6.70 (br s, 1H), 8.11 (s, 1H)

MS $^m/_z$:341 (M+1).

(i) *N*-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.026 g, 0.0075 mmol) was dissolved in DMF (1 mL). HATU (0.034 g, 0.090 mmol) and DIPEA (0.048 g, 0.38 mmol) were added and the reaction mixture was stirred at rt for 15 minutes before 1-phenylmethanesulfonamide (0.013 g, 0.075 mmol) was added. Stirring at rt was continued for 4h. According to LC/MS around half of the starting material had been converted at this point. Extra 1-phenylmethanesulfonamide (0.013 g, 0.075 mmol) was added and stirring at rt was continued over week-end (64h). LC/MS showed that still only around half of the starting material had been converted. Extra HATU (0.028 g, 0.075 mmol) was added and stirring at rt was continued for 5.5h further. According to LC/MS the reaction was complete at this point. Purification by preparative HPLC gave the pure product. Yield: 0.024 g (64 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, J =7.6 Hz, 3H), 1.74-1.61 (m, 2H), 1.90-1.81 (m, 2H), 2.58-2.54 (m, 1H), 2.79-2.72 (m, 5H), 3.17-3.08 (m, 2H), 4.51-4.44 (m, 2H), 4.70 (s, 2H), 7.04 (s, 1H), 7.34-7.29 (m, 2H), 7.45-7.39 (m, 3H), 8.38 (s, 1H), 11.62 (s, 1H)

MS $^m/_z$: 494 (M+1).

Example 38

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester

(a) Sodium propan-2-olate

Isopropyl alcohol (5 mL) was cooled to 0 °C. Sodium hydride (95%, 0.088 g, 3.48 mmol) was slowly added. The solution was used crude assuming a 100% conversion.

(b) 1-[3-Cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (0.400 g, 1.20 mmol) was dissolved in isopropyl alcohol (5 mL) and stirred at r.t for 10 minutes. Sodium propan-2-olate (0.286 g, 3.48 mmol) in isopropyl alcohol (5 mL) was added and the solution was stirred for 10 minutes. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The reaction mixture was concentrated under reduced pressure. The reaction mixture was concentrated under reduced pressure. The aqueous was washed with EtOAc (3 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (100% EtOAc to 100% EtOAc with 0.5% AcOH) yielded 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid as a solid. Yield: 0.133 g (51.0 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (6H, d, J = 6.2 Hz), 2.71 (3H, s), 3.59-3.67 (1H, m), 4.57-4.64 (4H, m), 5.15-5.24 (1H, m), 8.26 (1H, s).

MS $^m/_z$: 304 (M+1).

(c) 6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester

1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (0.047 g, 0.153 mmol), EDCI (0.035 g, 0.184 mmol) and HOBt (0.025 g, 0.184 mmol) were dissolved in DCM (1 mL) at r.t. The reaction mixture was stirred at r.t for 30 minutes and then 1-phenylmethanesulfonamide (0.032 g, 0.184 mmol) and DIPEA (0.134 mL, 0.767 mmol) were added. The reaction mixture was stirred at r.t for 18 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated NH_4Cl (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Trituration (4:1 Hexanes/CH_2Cl_2) gave 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester as a solid. Yield: 0.031 g (44.3 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 2.64 (3H, s), 3.52-3.59 (1H, m), 4.29-4.44 (4H, m), 4.75 (2H, m), 5.04-5.10 (1H, m), 7.32-7.40 (5H, m), 8.29 (1H, s), 11.8 (1H, s).

MS $^m/_z$: 457 (M+1).

Example 39

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid Isopropyl ester

(a) Isopropyl 2-((dimethylamino)methylene)-3-oxobutanoate

Isopropyl 3-oxobutanoate (200 mL, 1365 mmol) was stirred at r.t and dimethoxy-N,N-dimethylmethanamine (242 mL, 1706 mmol) was added drop-wise. The reaction mixture was allowed to stir at r.t overnight. The reaction mixture was concentrated under vacuum and then azeotroped with toluene (3 ´ 300 mL) and placed under high vacuum to afford isopropyl 2-((dimethylamino)methylene)-3-oxobutanoate as an oil, which was used without further purification. Yield: 272 g (100 %).

1H NMR (400 MHz, CDCl3): δ 1.30 (6H, d, J = 6.2 Hz), 2.32 (3H, s), 5.07-5.17 (1H, m); 7.64 (1H, s).

(b) Isopropyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

NaH (33.359 g, 834.07 mmol) was suspended in THF (700 mL) and 2-cyanoacetamide (58.905 g, 700.62 mmol) added portion-wise at r.t. When gas evolution had stopped a solution of isopropyl 2-((dimethylamino)methylene)-3-oxobutanoate (147.72 g, 667.25 mmol) in THF (300 mL) was added and the system stirred at r.t overnight. The reaction mixture was concentrated under reduced pressure and the solids dissolved in the minimum amount of to hot water. 1N HCl was added to the solution until pH 1 and the solids isolated by filtration. The solids were dried under high vacuum to afford isopropyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate as a solid, which was used without further purification. Yield: 123 g (84 %).

1H NMR (400 MHz, CDCl3): δ 1.37 (6H, d, J = 6.2 Hz), 2.84 (3H, s), 5.18-5.28 (1H, m), 8.50 (1H, s), 13.04 (1H, s).

MS $^m/_z$: 221 (M+1).

(c) Isopropyl 6-chloro-5-cyano-2-methylnicotinate

Isopropyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (123.04 g, 558.70 mmol) was suspended in POCl3 (204.58 mL, 2234.8 mmol) and heated at 100 oC for 5 h. The reaction mixture was cooled to r.t and concentrated under reduced pressure. The residue was diluted with DCM and poured onto ice. The bi-phasic mixture was stirred at r.t and slowly quenched with solid K2CO3 until all the POCl3 had hydrolysed. The aqueous was extracted into DCM and the organics, dried (MgSO4) and passed through a silica plug. The organics were concentrated under reduced pressure to afford isopropyl 6-chloro-5-cyano-2-methylnicotinate as a solid, which was used without further purification. Yield: 106 g (79 %).

1H NMR (400 MHz, CDCl3): δ 1.40 (6H, d, J = 6.2 Hz), 2.90 (3H, s), 5.23-5.30 (1H, m), 7.26 (1H, s), 8.46 (1H, s).

MS $^{m}/z$: 239 (M+1).

(d) 1-(3-Cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylicacid

Isopropyl 6-chloro-5-cyano-2-methylnicotinate (25.000 g, 104.75 mmol), piperidine-4-carboxylic acid (14.205 g, 109.98 mmol) and DIPEA (d 0.742) (54.735 mL, 314.24 mmol) were suspended in EtOH (200 mL) and heated at reflux for 1 h. The reaction mixture was cooled to r.t and added drop-wise to KHSO4 (71.316 g, 523.74 mmol) in water (2000 mL). The solids were collected by filtration and dried under vacuum to afford 1-(3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid as a solid, which was used without further purification. Yield: 35 g (100 %).

1H NMR (400 MHz, CDCl3): δ 1.35 (6H, d, J = 6.2 Hz), 1.81-1.93 (2H, m), 2.04-2.12 (2H, m), 2.67-2.74 (4H, m), 3.26-3.36 (2H, m), 4.53-4.62 (2H, m), 5.15-5.23 (1H, m), 8.32 (1H, s).

MS $^{m}/z$: 332 (M+1).

(e) 6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid Isopropyl ester

1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (30.00 g, 90.534 mmol), EDCI (26.03 g, 135.80 mmol), 1-phenylmethanesulfonamide (20.15 g, 117.69 mmol), HOBt (13.46g, 99.59 mmol) and DIPEA (47.308 mL, 271.60 mmol) were suspended in DCM (400 mL) and stirred for 5 minutes until homogenous. Then the reaction

mixture was refluxed for 4 h. The reaction mixture was cooled to r.t. and concentrated under reduced pressure. The crude reaction mixture was dissolved in EtOH (300 mL) and added drop-wise to a rapidly stirred solution of $KHSO_4$ (61.64 g, 452.67 mmol) in water (3000 mL). The product was collected by filtration, washed with water (3 x 400 mL) and dried under vaccum (44.00 g of dry product). The dry product was slurried in isopropyl alcohol (2000 mL) and stirred and heated at 50 °C for 2 h. The compound was isolated by filtration and dried under high vaccum to afford 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid Isopropyl ester as a solid. Yield: 37.41 g (85 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (6H, d, J = 6.2 Hz), 1.74-1.90 (4H, m), 2.37-2.45 (1H, m), 2.73 (3H, s), 3.10-3.17 (2H, m), 4.63-4.67 (4H, m), 5.17-5.23 (1H, m), 7.33-7.42 (5H, m), 7.48 (1H, br s), 8.33 (1H, s).

MS $^m/_z$: 485 (M+1).

The crystalline form obtained was characterised by the presence, in X-ray powder diffraction (XRPD) measurements, of peaks at about the 2-Theta and relative intensity values detailed in Table 2 below.

Peak label	Angle (2-Theta, °)	Relative Intensity (%)
a	4.945	100.0
b	7.142	3.4
c	9.337	26.8
d	9.863	15.9
e	10.324	18.1
f	12.960	2.9
g	13.398	17.6
h	14.327	60.9
i	14.800	4.1
j	17.096	4.6
k	18.344	6.5
l	18.668	5.0
m	19.094	9.6
n	19.800	5.2
o	20.130	15.1
p	20.674	20.2
q	21.073	7.3
r	21.865	25.6
s	22.563	7.8
t	23.033	18.4
u	23.849	13.7
v	24.209	6.4
x	24.789	17.9

y	25.458	6.1
z	26.055	5.0
aa	26.390	4.3
ab	27.072	6.3
ac	27.718	4.8
ad	28.721	9.8
af	29.783	10.5
ag	30.260	4.8
ah	30.840	4.8
ai	31.250	4.3
ak	34.511	4.3
al	36.014	4.4
am	37.174	4.1
an	37.855	3.5
ao	41.783	3.2
ap	43.320	4.9
aq	44.472	3.8
ar	45.346	3.1

Table 2: XRPD Peaks for Form **I** of **6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester**

Example 40

5-Cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinic acid ethyl ester and Sodium [(4-cyanobenzyl)sulfonyl]({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)azanide

(a) 1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid

Ethyl 6-chloro-5-cyano-2-methylnicotinate (3.00g, 13.35 mmol), Piperidine-4-carboxylic acid (1.897g, 14.69 mmol), and TEA (2.703 g, 26.71 mmol) were mixed and the mixture was refluxed for 10 minutes. LC/MS showed full conversion. The reaction mixture was evaporated, water/EtOAc 1:1 (100 mL) was added and the water phase was acidified to pH3. The EtOAc phase was separated and the water phase was extracted with an additional EtOAc (40 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated to give 3.8 g of a crude material.

Purification with preperative HPLC at pH=7 (0.1 M NH_4OAc/CH_3CN) with subsequent switch to pH=3 gave the pure product.Yield:1.9 g (45 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 7.1 Hz, 3H), 1.94-1.82 (m, 2H), 2.13-2.05 (m, 2H), 2.75-2.66 (m, 5H), 3.37-3.27 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.63-4.55 (m, 2H), 8.36 (s, 1H)

MS $^m/_z$: 318 (M+1).

(b) 5-Cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinic acid ethyl ester and Sodium [(4-cyanobenzyl)sulfonyl]({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)azanide

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.253 g, 0.8 mmol), 1-(4-cyanophenyl)methanesulfonamide (0.188 g, 0.96 mmol) and HATU (0.425 g, 1.12 mmol) were dissolved in DMF and TEA (0.161 g, 1.6 mmol) was added. After an additional 30 minutes DBU (0.243 g, 1.6 mmol) was added and the reaction was stirred at r.t over night. The reaction mixture was evaporated to dryness and the residue was partioned between EtOAc (40 mL) and water (40 mL). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give a yellow oil. Purification by preparative-HPLC (Kromasil C8 10uM, 50x300mm, 100mL/min , pH=7) afforded 0.091 g of pure 5-cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinic acid ethyl ester as a white solid. This solid was diluted in CH_3CN (6 mL) and 0,1 M NaOH (1,9 mL) and freeze dried to afford Sodium [(4-cyanobenzyl)sulfonyl]({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)azanide as a white solid. Yield: 0.101 g (24 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.2 Hz, 3H), 1.64-1.52 (m, 2H), 1.84-1.76 (m, 2H), 2.30-2.20 (m, 1H), 2.65 (s, 3H), 3.25-3.16 (m, 2H), 4.30-4.22 (q, J = 7.2 Hz, 2H), 4.36 (s, 2H), 4.48-4.40 (m, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 8.32 (s, 1H)

MS $^m/_z$: 496 (M+1)

Example 41

6-[4-({[(4-Chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester and Sodium [(4-chlorobenzyl)sulfonyl]({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)azanide

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.250 g, 0.79 mmol), 1-(4-chlorophenyl)methanesulfonamide (0.0.194 g, 0.94 mmol) and HATU (0.419 g, 1.10 mmol) were dissolved in DMF (5 mL) and TEA (0.161 g, 1.60 mmol) was added. After an additional 30 minutes BEMP (0.432 g, 1.58 mmol) was added and the

reaction was stirred at r.t over night. The reaction mixture was evaporated to dryness and the residue was partioned between EtOAc (30 mL) and water (40 mL). The phases were separated and the water phase was extracted with EtOAc (30 mL). The combined organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give an oil. Purification on preparative-HPLC (Kromasil C8 10uM, 50x300mm, 100mL/min , pH=7) afforded 0.101 g of pure 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester as a white solid. This solid was dissolved in CH_3CN (6 mL) and 0,1 M NaOH (2.5 mL) and freeze dried to afford sodium [(4-chlorobenzyl)sulfonyl]({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)azanide 101mg as a white solid. Yield: 0.118 g (28 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.2 Hz, 3H), 1.66-1.53 (m, 2H), 1.85-1.76 (m, 2H), 2.32-2.22 (m, 1H), 2.65 (s, 3H), 3.25-3.16 (m, 2H), 4.30-4.22 (m, 4H), 4.49-4.41 (m, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 8.32 (s, 1H)

MS $^m/_z$: 505 (M+1).

Example 42

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

A solution of ethyl 6-chloro-5-cyano-2-methylnicotinate (47.5 g, 211 mmol) and triethyl amine (58.36 g, 577 mmol) in EtOH (314 ml) was added to a stirred mixture of N-(benzylsulfonyl)piperidine-4-carboxamide (53.55 g, 189.7 mmol, See Example 31(b)) and EtOH (100 ml) at r.t. and the mixture was heated to 100 oC (bath temperature, 20-100 oC during 40 minutes, 100 °C 15 minutes then cool to r.t.) for 15 minutes. A solution of $KHSO_4$ (142.93 g in 900 mL water) was added to make the product precipitate out. The precipitate was filtered off and washed with water (2 x 250 mL) to give 87 g of a crude product (84 % pure). The crude product was slurried in 50 % EtOH (1200 mL) and heated to 50 oC (bath temperature) for 2 houra and 45 minutes followed by stirring over night at r.t. Filtration gave a crude product which was further washed by stirring with 25 % EtOH (1600 mL) at 50 °C for 2 hours followed by 20 % EtOH (1000 mL) at 50 °C for 2 hours. (An attempt to purify the material by using a 50% EtOH/water solution was not successful because it dissolved to much of the product). The solid obtained after the washings above (89 % pure) was dissolved in 700 mL EtOAc at 70 °C and the solution was left to crystallise at r.t. over night. The crystals was filtered off and washed with EtOAc (200 mL) to give pure 6-(4-

{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester as an orange solid (fine needles) after drying. Yield: 54.94 g of . Recrystallization of the solids from the motherliquor using EtOAc gave another 10.50 g. Yield 65.44 g (73%). The product can also be crystallized from $CHCl_3$.

^1H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 1.77-1.91 (4H, m), 2.37-2.44 (1H, m), 2.73 (3H, s), 3.10-3.17 (2H, m), 4.33 (2H, q, J = 7.0 Hz), 4.64-4.68 (4H, m), 7.36-7.41 (5H, m), 8.36 (1H, s).

MS $^m/_z$: 471(M+1).

The product obtained from crystallization in EtOAc (Form I) was characterised by the presence, in X-ray powder diffraction (XRPD) measurements, of peaks at about the 2-Theta and relative intensity values detailed in Table 3 below and the product obtained from crystallization in $CHCl_3$ (Form II) in Table 4 below.

Peak label	Angle (2-Theta, °)	Relative Intensity (%)
a	6.763	100.0
b	9.500	3.4
c	9.661	3.6
d	10.019	6.1
e	13.377	4.7
f	13.540	3.7
g	14.381	7.4
h	14.764	5.3
i	19.070	6.6
j	19.437	6.5
k	20.380	37.1
l	21.604	4.6
m	22.902	4.5
n	23.252	3.5
o	24.878	5.0
p	25.459	6.0
q	25.762	24.3
r	25.821	12.5
s	27.298	3.7
t	27.736	4.4
u	34.301	4.2
v	41.444	4.4

Table 3: XRPD Peaks for Form **I** of 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

Peak label	Angle (2-Theta, °)	Relative Intensity (%)
A	3.530	100.0
B	7.097	12.7
C	13.363	5.6
D	10.782	2.4
E	14.038	3.0
F	14.762	3.6
G	17.849	2.8
H	18.332	8.9
I	18.596	6.0
J	19.601	4.2
K	20.733	3.4
L	21.500	5.6
M	21.674	7.0
N	23.178	3.7
O	25.057	3.1
P	26.256	3.6
Q	26.738	2.9
R	33.755	2.5
S	41.031	2.9

Table 4: XRPD Peaks for Form **II** of 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

The crystalline forms may be further characterised by the presence of one or more of the additional properties listed below:

(i) for Form **I**

(I) when characterised by thermogravimetric analysis, a weight loss of approx. 0.8 % occurs in the range from 25°C up to 205°C, and/or

(II) when characterised by differential scanning calorimetry, at a heating rate of 10°C per minute in a closed cup with a pinhole under flowing nitrogen, a melting temperature (Tm) having an onset at about 194°C and/or an associated endotherm of melting of about 96 J/g; and/or

(III) when stored at 80% RH (ambient) less than 0.2 % moisture is adsorbed.

(i) for Form **II**

(I) when characterised by thermogravimetric analysis, a weight loss of approx. 0.2 % occurs in the range from 25°C up to 205°C, and/or

(II) when characterised by differential scanning calorimetry, at a heating rate of 10°C per minute in a closed cup with a pinhole under flowing nitrogen, a melting temperature (Tm) having an onset at about 193°C and/or an associated endotherm of melting of about 105 J/g.

Example 43

N-[(1,2-Benzisoxazol-3-ylmethyl)sulfonyl]-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.026 g, 0.076 mmol) was dissolved in DMF (1 mL). HATU (0.044 g, 0.057 mmol) and DIPEA (0.049 g, 0.11 mmol) were added and the reaction mixture was stirred at rt for 15 minutes before 1-(1,2-benzisoxazol-3-yl)methanesulfonamide (0.012 g, 0.057 mmol) was added. Stirring at rt was continued for 20h. Purification was done by preparative HPLC afforded the title compound. Yield: 0.014 g (46%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (t, J = 7.5 Hz, 3H), 1.66-1.54 (m, 2H), 1.84-1.77 (m, 2H), 2.29-2.20 (m, 1H), 2.77-2.70 (m, 5H), 3.21-3.12 (m, 2H), 4.40-4.32 (m, 2H), 4.72 (s, 2H), 7.01 (s, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 8.31 (s, 1H)

MS $^m/_z$: 535 (M+1).

Example 44

N-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]azetidine-3-carboxamide

(a) 1-[3-Cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid

2-chloro-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylnicotinonitrile (0.028 g, 0.11 mmol) was dissolved in dry EtOH (2 mL) in a Smith process vial. Azetidine-3-carboxylic acid (0.023 g, 0.23 mmol) and TEA (0.114 g, 1.13 mmol) were added and the sealed vial was heated in a microwave oven, single node heating, at 120 °C for 20 minutes. LC/MS showed full conversion. The reaction mixture was evaporated. 1M HCl (2 mL) was added. The mixture was extracted with DCM (3x2 mL) by using a phase separator. The organic phase were combined, dried with sodium sulphate and evaporated. This gave 0.033 g crude product.

Purification by flash chromatography on Si-gel with DCM/MeOH 39:1 + 1% formic acid as eluent gave the pure product. Yield: 0.026 g (74 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.5 Hz, 3H), 2.80-2.70 (m, 5H), 3.70-3.57 (m, 1H), 4.68-4.57 (m, 4H), 6.88 (br s, 1H), 8.20 (s, 1H)

MS $^m/_z$: 313 (M+1).

(b) *N*-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]azetidine-3-carboxamide

1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.012 g, 0.038 mmol) was dissolved in DMF (0.5 mL). HATU (0.018 g, 0.046 mmol) and DIPEA (0.025 g, 0.19 mmol) were added and the reaction mixture was stirred at rt for 30 minutes before 1-phenylmethanesulfonamide (0.008 g, 0.046 mmol) was added. Stirring at rt was continued for 18h. According to LC/MS no product had been formed at this point. EDCI ((0.007 g, 0.038 mmol) and HOBt (0.008 g, 0.058 mmol) were added and stirring at rt was continued for 28h further. Extra 1-phenylmethanesulfonamide (0.005 g, 0.029 mmol) was added and stirring at rt was continued over week-end (64h). According to LC/MS the reaction was complete at this point. Purification by preparative HPLC gave the pure product. Yield: 0.0005 g (5 %).

^{1}H NMR (400 MHz, CD_3Cl): δ 1.30 (t, J = 7.6 Hz, 3H), 2.74 (q, J = 7.6 Hz, 2H), 2.79 (s, 3H), 3.38-3.28 (m, 1H), 4.45-4.40 (m, 4H), 4.66 (s, 2H), 6.82 (s, 1H), 7.42-7.34 (m, 5H), 8.21 (s, 1H)

MS $^m/_z$: 466 (M+1).

Example 45

***N*-[(4-Chlorobenzyl)sulfonyl]-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide**

1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.026 g, 0.075 mmol) was dissolved in DMF (1 mL). HATU (0.019 g, 0.090 mmol) and DIPEA (0.048 g, 0.38 mmol) were added and the reaction mixture was stirred at rt for 15 minutes before 1-(4-chlorophenyl)methanesulfonamide (0.019 g, 0.090 mmol) was added. Stirring at rt was continued for 27.5h. According to LC/MS the reaction was incomplete at this point. Extra HATU (0.028 g, 0.075 mmol) and 1-(4-chlorophenyl)methanesulfonamide (0.014 g, 0.068 mmol) were added and stirring at rt was continued for 26h further. LC/MS

showed the reaction to be almost complete. Purification by preparative HPLC gave the pure product. Yield: 0.008 g (18 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30-1.22 (t, J = 7.5 Hz, 3H), 1.74- 1.61 (m, 2H), 1.91-1.82 (m, 2H), 2.64-2.55 (m, 1H), 2.80-2.71 (m, 5H), 3.18-3.08 (m, 2H), 4.52-4.44 (m, 2H), 4.74 (s, 2H), 7.04 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 8.35 (s,1H), 11.65 (s, 1H),

MS $^m/_z$: 528 (M+1).

Example 46

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid (20.00 g, 69.14 mmol), EDCI (19.88 g, 103.7 mmol), 1-phenyl-methane sulfonamide (15.39 g, 89.88 mmol), HOBt (10.276 g, 76.049 mmol) and DIPEA (36.127 mL, 207.41 mmol) were suspended in DCM (500 mL) and stirred at r.t for 5 minutes until homo genous. Then the reaction mixture was refluxed for 3 h. The reaction mixture was cooled to r.t and concentrated under reduced pressure. The crude reaction mixture was dissolved in EtOH (400 mL) and added drop-wise to a rapidly stirred solution of $KHSO_4$ (47.07 g, 345.68 mmol) in water (4000 mL). The product was collected by filtration, washed with water (3 x 500 mL) and dried under vaccum (30.61 g of dry product). The dry product was slurried in EtOH (1500 mL) and stirred and heated at 50 ^{0}C for 1 h. The compound was isolated by filtration and dried under high vaccum to afford the desired material as crystals.Yield: 27.65 g (90%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.57 (s, 3H), 3.43 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.23 (t, J = 7.1 Hz, 2H), 4.34 (t, J = 8.9 Hz, 2H), 4.68 (s, 2H), 7.29 (m, 5H), 8.33 (s, 1H), 11.75 (s, 1H)

MS $^m/_z$: 443 (M+1)

The crystals were characterised by the presence, in X-ray powder diffraction (XRPD) measurements, of peaks at about the 2-Theta and relative intensity values detailed in Table 5 below.

Peak label	Angle (2-Theta, °)	Relative Intensity (%)
a	5.388	100.0
b	7.293	12.0

c	10.049	6.2
d	10.796	28.8
e	13.263	4.1
f	13.949	16.4
g	14.597	21.8
h	16.177	3.1
i	17.691	3.8
j	18.888	5.0
k	20.053	10.7
l	20.477	12.6
m	20.990	15.9
n	21.608	26.7
o	22.577	9.1
p	23.991	16.0
q	24.872	9.6
r	26.203	7.9
s	26.761	7.7
t	27.188	11.8
u	31.221	4.9
v	34.030	5.6

Table 5: XRPD Peaks for Form **I** of 5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

Example 47

Ethyl 5-cyano-6-{3-[({[3-(4-methoxyphenoxy)propyl]sulfonyl}amino) carbonyl]azetidin-1-yl}-2-methylnicotinate

Prepared according to method A using 3-(4-methoxyphenoxy)propane-1-sulfonamide (0.105 g crude, 0.37 mmol).Yield: 0.041 g (32%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.03 (quintet, J = 6.6 Hz, 2H), 2.54 (s, 3H), 3.59 (s, 3H), 3.6 - 3.4 (m, 3H overlapped by water), 3.94 (t, J = 6.0 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.27 (m, 2H), 4.38 (t, J = 8.6 Hz, 2H), 6.75 (m, 4H), 8.21 (s, 1H)
MS $^m/_z$: 517 (M+1)

Example 48

Ethyl 4-amino-6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloronicotinate

(a) Ethyl 4-amino-6-(3-(tert-butoxycarbonyl)azetidin-1-yl)-5-chloronicotinate

Ethyl 4-amino-5,6-dichloronicotinate (0.560 g, 2.38 mmol) was dissolved in DMA (5 mL) and tert-butyl azetidine-3-carboxylate (0.65 g, 4.1 mmol) and DIPEA (1.2 mL, 7.1 mmol) were added. The reaction was heated at 90 °C. After 4hr, additional tert-butyl azetidine-3-carboxylate (0.32 g, 2.0 mmol) and DIPEA (1.0 mL, 5.9 mmol) were added and heating was continued. After 2 hr additional tert-butyl azetidine-3-carboxylate (0.45 g, 2.9 mmol) and DIPEA (1.0 mL, 5.9 mmol) were added. The reaction was heated an additional 1.5 hr and then the reaction was cooled and concentrated under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with saturated NH_4Cl (2 × 75 mL), brine and dried ($MgSO_4$). The solution was then concentrated under reduced pressure and the crude product was purified with flash chromatography (DCM to 5% EtOAc/DCM) to provide ethyl 4-amino-6-(3-(tert-butoxycarbonyl)azetidin-1-yl)-5-chloronicotinate as a solid. Yield: 0.38 g (45 %).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, J = 7.1 Hz), 1.48 (9H, s), 3.34-3.42 (1H, m), 4.30 (2H, q, J = 7.1 Hz), 4.40-4.48 (4H, m), 8.53 (1H, s).
MS $^m/_z$: 356 (M+1).

(b) 1-(4-Amino-3-chloro-5-(ethoxycarbonyl)pyridin-2-yl)azetidine-3-carboxylic acid hydrochloride

Ethyl 6-(3-(tert-butoxycarbonyl)azetidin-1-yl)-4-amino-5-chloronicotinate (0.37 g, 1.0 mmol) was dissolved in a solution of 4M HCl in dioxane (5 mL). After 14 hr at room temperature the reaction was concentrated under reduced pressure and azeotroped with DCM and EtOAc to provide 1-(4-amino-3-chloro-5-(ethoxycarbonyl)pyridin-2-yl)azetidine-3-carboxylic acid hydrochloride which was used without further purification. Yield 0.35 g, (100%).

(c) Ethyl 4-amino-6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloronicotinate

1-(4-Amino-3-chloro-5-(ethoxycarbonyl)pyridin-2-yl)azetidine-3-carboxylic acid hydrochloride (0.077 g, 0.23 mmol) was combined with EDCI (0.057 g, 0.30 mmol) and HOBt (0.040 g, 0.30 mmol) in DCM (4 mL). Phenylmethanesulfonamide (0.055 g, 0.32 mmol) was then added, followed by DIPEA (0.24 mL, 1.4 mmol). The reaction was allowed to stir 14 hr. The reaction was then partitioned between EtOAc (75 mL) and NH_4Cl solution (20 mL). The organic was washed with NH_4Cl (20 mL) and then brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by column chromatography (30 to 50 % EtOAc/hexanes, then added 0.5% HOAc). Ethyl 4-

amino-6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloronicotinate was isolated as a solid. Yield: 0.070 g (67 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 3.19-3.26 (1H, m), 4.28-4.38 (6H, m), 4.70 (2H, s), 7.38-7.40 (5H, m), 8.53 (1H, s).

MS $^m/_z$: 453 (M+1).

Example 49

Ethyl 5-cyano-2-methyl-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid (0.058 g, 0.2 mmol) was dissolved in DMF (1 mL) and HATU (0.099 g, 0.26 mmol), DIPEA (0.170 mL, 1 mmol) and 1-(3-methylphenyl)methanesulfonamide (0.037 g, 0.2 mmol) was added at r.t. and the reaction was stirred for 30 h. The solvent was removed in vaccuo and the residue was purified by preparative HPLC (Kromasil C8 10 µM , 20 x 100 mm column, flow: 30 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) to give the pure product. Yield: 0.019 g (15 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 2.65 (s, 3H), 3.53-3.62 (m, 1H), 4.21-4.34 (m, 4H), 4.39-4.47 (m, 2H), 4.72 (s, 2H), 7.13-7.32 (m, 4H), 8.33 (s, 1H), 11.81 (br s, 1H).

MS $^m/_z$: 457 (M+1).

Example 50

2,2-Dimethylpropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

(a) Ethyl 6-(4-(tert-butoxycarbonyl)piperidin-1-yl)-5-cyano-2-methylnicotinate

A solution of ethyl 6-chloro-5-cyano-2-methylnicotinate (6.00 g, 26.7 mmol), *tert*-butyl piperidine-4-carboxylate hydrochloride (6.51, 29.4 mmol) and DIPEA (23.3 mL, 134 mmol) in DMA (50 mL) were heated to 80 °C for 2 h. After cooling to r.t, the reaction mixture was diluted with EtOAc (300 mL), washed with saturated NH_4Cl (4 x 50 mL), brine (50 mL), dried ($MgSO_4$), passed through silica gel and concentrated. Flash chromatography produced ethyl 6-(4-(tert-butoxycarbonyl)piperidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 8.85 g (89 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.45 (9H, s), 1.75-1.84 (2H, m), 1.99-2.03 (2H, m), 2.49-2.57 (1H, m), 2.72 (3H, s), 3.24-3.31 (2H, m), 4.31 (2H, q, J = 7.1 Hz), 4.55-4.60 (2H, m), 8.34 (1H, s).
MS $^m/_Z$: 374 (M+1).

(b) 6-(4-(*tert*-Butoxycarbonyl)piperidin-1-yl)-5-cyano-2-methylnicotinic acid
To a solution of ethyl 6-(4-(tert-butoxycarbonyl)piperidin-1-yl)-5-cyano-2-methylnicotinate (6.65 g, 17.8 mmol) in THF 50 mL was added aqueous LiOH (1.0 M, 107 mL, 107 mmol) and the mixture was heated to reflux for 5 h. After cooling to r.t , the reaction was acidified to pH 3.5 with 2 M HCl and extracted into EtOAc (4 x 50 mL). The organic extracts were washed with brine, dried ($MgSO_4$), passed through silica gel and concentrated. Flash chromatography (20% EtOAc/hexanes with 1% HOAc) furnished 6-(4-(*tert*-butoxycarbonyl)piperidin-1-yl)-5-cyano-2-methylnicotinic acid as a solid. Yield: 1.8 g (29 %)
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (9H, s), 1.53-1.63 92H, m), 1.90-1.94 (2H, m), 2.55-2.60 (1H, m), 2.64 (3H, s), 3.21-3.28 2H, m), 4.40-4.44 (2H, m), 8.30 (1H, s), 12.91 (1H, br s).
MS $^m/_Z$: 350 (M+1).

(c) 2,2-Dimethylpropyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate
A solution of 6-(4-(*tert*-butoxycarbonyl)piperidin-1-yl)-5-cyano-2-methylnicotinic acid (0.845 g, 2.45 mmol), neopentyl alchol (1.30 g, 14.7 mmol), EDCI (2.11 g, 11.0 mmol), HOBt (0.496 g, 3.67 mmol) and DIPEA (0.852 mL, 4.89 mmol) were heated to 80 °C for 2 days. The reaction mixture was diluted with EtOAc (50 mL), washed with saturatued NH_4Cl (3 x 30 mL), brine, dried ($MgSO_4$), passed through silica gel and concentrated. Flash chromatography (3 % EtOAc/hexanes) yielded 2,2-dimethylpropyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate as a solid. Yield: 1.02 g (41 %).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (9H, s), 1.46 (9H, s), 1.76-1.85 (2H, m), 2.00-2.03 (2H, m), 2.49-2.57 (1H, m), 2.73 (3H, M), 3.25-3.31 (2H, m), 3.96 (2H, s), 4.56-4.60 (2H, m), 8.32 (1H, s).
MS $^m/_Z$: 416 (M+1).

(d) 1-{3-Cyano-5-[(2,2-dimethylpropoxy)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid

To a solution of 2,2-dimethylpropyl 6-[4-(tert-butoxycarbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate (0.415 g, 0.999 mmol) in DCM (10 mL) at 0 °C was added TFA (10 mL) and the reaction mixture was stirred for 2 h. Concentration produced 1-{3-cyano-5-[(2,2-dimethylpropoxy)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid which was used crude assuming 100 % conversion.

MS $^{m}/_{z}$: 513 (M+1).

(e) 2,2-Dimethylpropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

A solution of 1-{3-cyano-5-[(2,2-dimethylpropoxy)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid (0.120 g, 0.334 mmol), EDCI (0.0832 g, 0.434 mmol) and DIPEA (0.291 mL, 1.67 mmol) in DCM (3 mL) were stirred at r.t for 30 minutes. Phenylmethanesulfonamide (0.0686 g, 0.401 mmol) was added and stirring was continued for 18 h. Additional EDCI (0.0832 g, 0.434 mmol) and phenylmethanesulfonamide (0.0686 g, 0.401 mmol) were added and the reaction mixture was stirred for 3 days, diluted with EtOAc (50 mL), washed with saturated NH_4Cl (3 x 30 mL), brine, dried ($MgSO_4$) and concentrated. Flash chromatography (1:4 EtOAc/hexanes with 1% HOAc) followed by reverse phase HPLC purification afforded 2,2-dimethylpropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.0175 g (10 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (9H, s), 1.78-1.91 (4H, m), 2.83-2.46 (1H, m), 2.74 (3H, s), 3.11-3.18 (2H, s), 3.97 (2H, s), 4.65-4.70 (4H, m), 7.34-7.35 (2H, m), 7.39-7.41 (3H, m), 8.34 (1H, s).

MS $^{m}/_{z}$: 513 (M+1).

Example 51

Ethyl 5-cyano-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Thionyl chloride (0.119 g, 1 mmol) was added to a solution of 1-[3-Cyano-5-(ethoxycarbonyl)-6-methylpyridine-2-yl]azetidine-3-carboxylic acid (0.058 g, 0.2 mmol) in DCM (1 mL) at 0 ^{0}C and the reaction mixture was allowed to reach r.t and stirred for 30

minutes. The DCM and excess thionyl chloride was evaporated (the residue was re-dissolved in DCM (1 mL) and evaporated, this was repeated once) and the residue was dissolved in pyridine at 0 ^{0}C followed by addition of 1-(4-methylphenyl)methanesulfonamide (0.044 g, 0.24 mmol). After stirring for 2 h at r.t. DMAP (a few crystals) was added and the stirring was continued for 19 h. BEMP (0.055 g, 0.2 mmol) was added and the stirring was continued for 22 h at r.t. LC/MS showed that only the starting materials were present. HATU (0.152 g, 0.4 mmol) and DIPEA (0.259g, 2 mmol) was added to the mixture at r.t. and the stirring was continued for 20 h at r.t. The solvent was removed in vaccuo and the residue was purified by preparative HPLC (Kromasil C8 10 µM , 20 x 100 mm column, flow: 30 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) to give the pure product. Yield: 0.019 g (15 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, *J*= 7.0 Hz, 3H), 2.32 (s, 3H), 2.66 (s, 3H), 3.51-3.60 (m, 1H), 4.20-4.37 (m, 4H), 4.38-4.47 (m, 2H), 4.70 (s, 2H), 7.17-7.28 (m, 4H), 8.34 (s, 1H), 11.77 (br s, 1H).
MS $^m/_z$: 457 (M+1).

Example 52

Ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate and Sodium ({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)[(4-fluorobenzyl)sulfonyl]azanide

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.350 g, 1.10 mmol), EDCI (0.274 g, 1.43 mmol)), 1-(4-fluorophenyl)methanesulfonamide (0.271 g, 1.43 mmol) and HOBt (0.194 g, 1.43 mmol) were suspended in DCM (8 mL) and DIPEA (0.713 g, 5.51 mmol) was added to the slurry. The reaction became homogenous after 30 minutes and the stirring was continued over night. The solvent was removed in vaccuo and the residue was dissolved in EtOAc(20 mL). The organic phase was washed with 0.5 M $KHSO_4$ (5 mL), water (5 mL) and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8) afforded 0.429 g of ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate as a white solid.
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (t, *J*= 7.2 Hz, 3H), 1.56-1.69 (m, 2H), 1.80-1.88 (m, 2H), 2.57 (m, 1H), 2.64 (s, 3H), 3.13 (m, 2H), 4.24 (q, *J*=7.2 Hz, 2H), 4.53 (m, 2H), 4.68 (s, 2H), 7.20-7.27 (m, 2H), 7.30-7.35 (m, 2H), 8.33 (s, 1H), 11.60 (br s, 1H).

This solid was dissolved in CH_3CN (3 mL), 0.1 M NaOH(8.5 mL) and finally freeze dried to give sodium ({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)[(4-fluorobenzyl)sulfonyl]azanide as a white solid. Yield: 0.444 g (76 %).

Example 53

Ethyl 6-[4-({[(3-bromobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

HATU (0.205 g, 0.54 mmol) and DIPEA (0.194 g, 1.5 mmol) was added to a stirred solution of 1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.095 g, 0.30 mmol) in DMF (1.5 mL) at r.t. followed by 1-(3-bromophenyl)methanesulfonamide (0.090 g, 0.36 mmol) and the reaction was stirred for 16 h. The solvent was removed and the the crude product was purified by preaparative HPLC (Kromasil C8, 250 mm x 50 mm i.d. flow 50 mL/minute, using a linear gradient of 0.1 M NH_4OAc/CH_3CN 95/5 to 0/100 over 40 minutes. Yield: 0.035 g (21 %).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (t, J = 7.0 Hz, 3H), 1.58-1.74 (m, 2H), 1.80-1.90 (m, 2H), 2.00-2.15 (m, 1H), 2.66 (s, 3H), 3.10-3.22 (m, 2H), 4.27 (q, J = 7.0 Hz, 2H), 4.51-4.61 (m, 2H), 4.75 (s, 2H), 7.29-7.35 (m, 1H), 7.37-7.44 (m, 1H), 7.47-7.51 (m, 1H), 7.60-7.66 (m, 1H), 8.36 (s, 1H), 11.68 (br s, 1H).

MS $^m/_z$: 550 (M+1).

Example 54

Cyclopropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

(a) Benzyl 2-[(dimethylamino)methylene]-3-oxobutanoate

Benzyl 3-oxobutanoate (82 mL, 475mmol) was stirred at r.t and 1,1-dimethoxy-N,N-dimethylmethanamine (76 mL, 570 mmol) was added drop-wise. The reaction mixture was allowed to stir at r.t overnight. The reaction mixture was concentrated under vacuum and then azeotroped with toluene (3 × 200 mL) and placed under high vacuum to afford Benzyl 2-[(dimethylamino)methylene]-3-oxobutanoateas an oil, which was used without further purification. Yield: 117 g (100 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, s), 3.02 (6H, br s), 5.22 (2H, s), 7.29-7.43 (5H, m), 7.70 (1H, s).

(b) Benzyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

NaH (19.9 g, 498 mmol) was added to a stirred r.t suspension of 2-cyanoacetamide (39.9 g, 475 mmol) in THF (1 L). The reaction mixture was stirred at r.t until gas evolution stopped. Benzyl 2-[(dimethylamino)methylene]-3-oxobutanoateas (117.4 g, 474.7 mmol) was added portion-wise and the reaction mixture stirred at r.t overnight. 1N HCl was added and the system stirred at r.t for 1 h and then the reaction mixture was diluted with EtOAc and extracted. The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford benzyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate as a solid, which was used without further purification. Yield: 111 g (88 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.63 (3H, s), 5.29 (2H, s), 7.34-7.47 (5H, m), 8.72 (1H, s), 12.82 (1H, s).

MS $^m/_z$: 267 (M-1).

(c) 6-Chloro-5-cyano-2-methylnicotinic acid

Benzyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate was suspended in $POCl_3$ (43.44 mL, 474.5 mmol) and heated at 100 °C overnight. The reaction mixture was cooled to r.t and poured onto ice. The aqueous was neutralized with solid $NaHCO_3$ and extracted into DCM. The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the material. Flash chromatography (gradient elution 30 - 50 % EtOAc / Hexanes, 0.5 % AcOH) gave crude 6-Chloro-5-cyano-2-methylnicotinic acid as a solid. Yield: 24.2 g (26 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (3H, s), 8.50 (1H, s).

MS $^m/_z$: 195 (M-1).

(d) 6-Chloro-5-cyano-2-methylnicotinoyl chloride

6-chloro-5-cyano-2-methylnicotinic acid (4.00 g, 20.4 mmol) and oxalyl chloride (2.66 mL, 30.5 mmol) were suspended in DCM (75 mL) and heated at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure and azeotroped with Hexanes and Toluene. The reaction mixture was then concentrated under reduced pressure to afford the crude 6-chloro-5-cyano-2-methylnicotinoyl chloride, which was used without further purification.

(e) Cyclopropanol

Cyclopropanol prepared according to the literature: *J. Org. Chem.* 41(7), 1237-40, 1976. and *J. Org. Chem* 45(21), 4129-35, 1980.

(e) Cyclopropyl 6-chloro-5-cyano-2-methylnicotinate

6-Chloro-5-cyano-2-methylnicotinoyl chloride (2.00 g, 9.30 mmol), cyclopropanol (0.54 mL, 9.30 mmol) and DIPEA (1.62 mL, 9.30 mmol), were suspended in DCM (40 mL) and stirred at r.t for 16 h. Water (40 mL) was added to the solution and stirred for 5 minutes. The layers were separated and the organics were washed with water (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (40% DCM in Hexanes) afforded cyclopropyl 6-chloro-5-cyano-2-methylnicotinate as a solid. Yield: 0.500 g (23 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85-0.92 (4H, m), 2.90 (3H, s), 4.38-4.45 (1H, m), 8.41 (1H, s).

(f) 1-(3-Cyano-5-(cyclopropoxycarbonyl)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid

Cyclopropyl 6-chloro-5-cyano-2-methylnicotinate (0.084 g, 0.354 mmol), 3-azetidinecarboxylic acid (0.090 g, 0.887 mmol), and DIPEA (0.442 mL, 2.54 mmol), were suspended in EtOH (4 mL) and then refluxed for 1 h. The reaction mixture was cooled to r.t and concentrated under reduced pressure. EtOAc (50 mL) was added and the reaction mixture was washed with saturated NH_4Cl (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave 1-(3-cyano-5-(cyclopropoxycarbonyl)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid as a solid. Yield: 0.180 g (71 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.83 (4H, m), 2.61 (3H, s), 3.50-3.60 (1H, m), 4.21-4.27 (1H, m), 4.31-4.39 (2H, m), 4.45-4.54 (2H, m), 8.26 (1H, s), 12.8 (1H, s).

(g) Cyclopropyl 6-(3-(benzylsulfonylcarbamoyl)azetidin-1-yl)-5-cyano-2-methylnicotinate

1-(3-cyano-5-(cyclopropoxycarbonyl)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid (0.165 g, 0.548 mmol), EDCI (0.157 g, 0.821 mmol), phenylmethanesulfonamide (0.113 g, 0.657 mmol), HOBt (0.081 g, 0.602 mmol) and DIPEA (0.286 mL, 1.64 mmol) were suspended in DCM (10 mL) and then refluxed for 3 h. The reaction mixture was cooled to r.t and concentrated under reduced pressure. The crude reaction mixture was dissolved in IPA (10 mL) and added drop-wise to a rapidly stirring solution of $KHSO_4$ (0.373 g, 2.74 mmol) in water (100 mL). The product was collected by filtration, washed with water (3 x 20 mL) and dried under vacuum. The dry product was slurried in IPA (100 mL), stirred and heated at 50 °C for 1 h. The solution was then cooled at 0 °C for 3 h. The material was isolated by filtration and dried under high vacuum to give cyclopropyl 6-(3-(benzylsulfonylcarbamoyl)azetidin-1-yl)-5-cyano-2-methylnicotinate as a solid, which was used without further purification. Yield: 0.146 g (53 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.83 (4H, m), 2.63 (3H, s), 3.52-3.59 (1H, m), 4.22-4.47 (5H, m), 4.75 (2H, s), 7.31-7.43 (5H, m), 8.28 (1H, s), 11.8 (1H, s).

MS $^m/_z$: 455 (M+1).

Example 55

2,2,2-Trifluoroethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

(a) 2,2,2-Trifluoroethyl 6-chloro-5-cyano-2-methylnicotinate

Crude 6-chloro-5-cyano-2-methylnicotinoyl chloride (0.500 g, 2.32 mmol), 2,2,2-trifluoroethanol (1.69 mL, 23.2 mmol) and DIPEA (2.02 mL, 11.63 mmol) were suspended in DCM (10 mL) and stirred at r.t until complete consumption of starting material was observed by HPLC analysis. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$. The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude material. Flash chromatography (100% DCM) gave 2,2,2-trifluoroethyl 6-chloro-5-cyano-2-methylnicotinate as a solid. Yield: 0.155 g (24 %).

(b) 2,2,2-Trifluoroethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-Trifluoroethyl 6-chloro-5-cyano-2-methylnicotinate (0.057 g, 0.204 mmol), N-(benzylsulfonyl)piperidine-4-carboxamide hydrochloride (0.085 g, 0.266 mmol,See Example

34(d)) and DIPEA (0.18 mL, 1.023 mmol) were suspended in DMF (5 mL) and stirred at r.t for 4 h. The reaction mixture was added drop-wise to a stirred solution of $KHSO_4$ (0.195 g, 1.43 mmol) in water (50 mL). The product was collected by filtration and dried under high vacuum to give 2,2,2-trifluoroethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield 0.095 g (88 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.58-1.72 (2H, m), 1.81-1.91 (2H, m), 2.55-2.69 (4H, m), 3.13-3.24 (2H, m), 4.54-4.64 (2H, m), 4.70 (2H, s), 4.90-4.98 (2H, m), 7.26-7.33 (2H, m), 7.36-7.45 (3H, m), 8.34 (1H, s), 11.61 (1H, s).

MS $^m/_z$: 525 (M+1).

Example 56

2,2,2-Trifluoroethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

(a) 1-(3-Cyano-6-methyl-5-((2,2,2-trifluoroethoxy)carbonyl)pyridin-2-yl)azetidine-3-carboxylic acid

2,2,2-Trifluoroethyl 6-chloro-5-cyano-2-methylnicotinate (0.155 g, 0.556 mmol), azetidine-3-carboxylic acid (0.068 g, 0.67 mmol) and DIPEA (0.485 mL, 2.78 mmol) were suspended in EtOH (10 mL) and heated at Reflux for 1 h. The reaction mixture was cooled to r.t and added drop-wise to $KHSO_4$ (0.53 g, 3.89 mmol) in water (100 mL). The solids were collected by filtration and dried under vacuum to afford the crude desired material. Flash chromatography (eluant 30 - 50 % EtOAc / Hexanes 0.5 % AcOH) gave 1-(3-Cyano-6-methyl-5-((2,2,2-trifluoroethoxy)carbonyl)pyridin-2-yl)azetidine-3-carboxylic acid as a solid. Yield: 0.136 g (71 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (3H, s), 3.60-3.69 (1H, m), 4.58-4.70 (6H, m), 8.29 (1H, s).

MS $^m/_z$: 344 (M+1).

(b) 2,2,2-Trifluoroethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

1-(3-Cyano-6-methyl-5-((2,2,2-trifluoroethoxy)carbonyl)pyridin-2-yl)azetidine-3-carboxylic acid (0.068 g, 0.198 mmol), phenylmethanesulfonamide (0.044 g, 0.258 mmol), EDCI (0.057 g, 0.297 mmol), HOBt (0.029 g, 0.218 mmol) and DIPEA (0.10 mL, 0.59 mmol) were

suspended in DCM (5 mL) and heated at reflux for 4 h. The reaction mixture was diluted with DCM and washed with saturated NH_4Cl and the organics dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude material. Flash chromatography (gradient elution 30 - 50 % EtOAc / Hexanes, 0.5 % AcOH) gave 2,2,2-trifluoroethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.061 g (62 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.52-3.62 (1H, m), 4.28-4.38 (2H, m), 4.39-4.51 (2H, m), 4.76 (2H, s), 4.86-4.97 (2H, m), 7.30-7.43 (5H, m), 8.13 (1H, s), 11.83 (1H, s).
MS $^m/_z$: 497 (M+1).

Example 57

2,2,2-Trifluoroethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate

1-(3-Cyano-6-methyl-5-((2,2,2-trifluoroethoxy)carbonyl)pyridin-2-yl)azetidine-3-carboxylic acid (0.068 g, 0.198 mmol), (4-chlorophenyl)methanesulfonamide (0.053 g, 0.258 mmol), EDCI (0.057 g, 0.297 mmol), HOBt (0.0294 g, 0.218 mmol) and DIPEA (0.104 mL, 0.594 mmol) were suspended in DCM (5 mL) and heated at reflux for 4 h. The reaction mixure was diluted with DCM and washed with saturated NH_4Cl and the organics dried, $MgSO_4$ and concentrated under reduced pressure to afford the crude material. Flash chromatography (gradient elution 30 - 50 % EtOAc / Hexanes, 0.5 % AcOH) gave 2,2,2-trifluoroethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate as a solid. Yield: 0.067 g (64 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.54-3.64 (1H, m), 4.27-4.38 (2H, m), 4.41-4.52 (2H, m), 4.78 (2H, s), 4.85-4.97 (2H, m), 7.33-7.41 (2H, m), 7.42-7.50 (2H, m), 8.31 (1H, s), 11.85 (1H, s).
MS $^m/_z$: 531 (M+1).

Example 58

Cyclopropyl 6-(4-(benzylsulfonylcarbamoyl)piperidin-1-yl)-5-cyano-2-methylnicotinate

Cyclopropyl 6-chloro-5-cyano-2-methylnicotinate (0.084 g, 0.354 mmol), N-(benzylsulfonyl)piperidine-4-carboxamide hydrochloride (0.100 g, 0.354 mmol, See Example 34(d)), and DIPEA (0.185 mL, 1.06 mmol), were suspended in EtOH (3 mL) and then refluxed for 1 h. The reaction mixture was cooled to r.t and concentrated under reduced

pressure. EtOAc (50 mL) was added and the reaction mixture was washed with saturated NH_4Cl (2 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave cyclopropyl 6-(4-(benzylsulfonylcarbamoyl)piperidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.098 g (57.2 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.83 (4H, m), 1.59-1.71 (2H, m), 1.79-1.88 (2H, m), 2.54-2.61 (1H, m), 2.64 (3H, s), 3.08-3.20 (2H, m), 4.21-4.30 (1H, m), 4.49-4.59 (2H, m), 4.70 (2H, s), 7.26-7.33 (2H, m), 7.73-7.44 (3H, m), 8.31 (1H, s), 11.6 (1H, s).

MS $^m/_z$: 483 (M+1).

Example 59

Cyclobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester (0.080 g, 0.181 mmol) and molecular sieves (4Å, 0.100 g) were dissolved in cyclobutanol (1 mL) and DMSO (2 mL) and stirred at room temperature for 1 h. Sodium hydride (95 %, 0.014 g, 0.542 mmol) was added to the reaction mixture and stirred for 2 h at room temperature. EtOAc (30 mL) was added and the reaction mixture was filtered through celite. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The reaction mixture was concentrated under reduced pressure. WATER (30 mL) was added and the aqueous was washed with EtOAc (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (20 % EtOAc in Hexanes with 0.1 % AcOH) and Trituration (1 / 1 – Et_2O / Hexanes) gave cyclobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.020 g (23 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.61-1.71 (1H, m), 1.77-1.85 (1H, m), 2.10-2.22 (2H, m), 2.29-2.40 (2H, m), 2.64 (3H, s), 3.53-3.60 (1H, m), 4.27-4.35 (2H, m), 4.38-4.46 (2H, m), 4.75 (2H, s), 5.04-5.13 (1H, m), 7.31-7.43 (5H, m), 8.35 (1H, s), 11.8 (1H, s).

MS $^m/_z$: 469 (M+1).

Example 60

2-Hydroxyethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester and molecular sieves (4Å, 0.100 g) were dissolved in ethylene glycol (2 mL) and DMSO (2 mL) and stirred at room temperature for 1 h. Sodium hydride (95 %, 0.017 g, 0.678 mmol) was added to the reaction mixture and stirred for 2 h at room temperature. EtOAc (50 mL) was added and the reaction mixture was filtered through celite. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The reaction mixture was concentrated under reduced pressure. Water (30 mL) was added and the aqueous was washed with EtOAc (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Heating (50 % EtOAc in Hexanes at 50 °C) gave 2-hydroxyethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinateas a solid. Yield: 0.038 g (37.1 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.54-3.60 (1H, m), 3.65-3.71 (2H, m), 4.16-4.23 (2H, m), 4.28-4.33 (2H, m), 4.39-4.48 (2H, m), 4.76 (2H, s), 4.91-4.99 (1H, m), 7.31-7.43 (5H, m), 8.46 (1H, s), 11.8 (1H, s).

MS $^m/_z$: 459 (M+1).

Example 61

Benzyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester (0.100 g, 0.226 mmol) and molecular sieves (4Å, 0.100 g) were dissolved in benzyl alcohol (5 mL) and DMSO (1 mL) and stirred at room temperature for 1 h. Sodium hydride (95 %, 0.017 g, 0.678 mmol) was added to the reaction mixture and stirred for 60 h at room temperature. EtOAc (50 mL) was added and the reaction mixture was filtered through celite. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The reaction mixture was concentrated under reduced pressure. Water (30 mL) was added and the aqueous was washed with EtOAc (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (Hexanes then 20 % EtOAc in Hexanes, and 20 % EtOAc in Hexanes with 0.1 % AcOH) gave Benzyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.013 g (12 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.51-3.59 (1H, m), 4.27-4.47 (4H, m), 4.75 (2H, s), 5.28 (2H, s), 7.29-7.52 (10H, m), 8.35 (1H, s), 11.8 (1H, s).

Example 62

Isopropyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

(a) 1-(3,4-Dichlorophenyl)methanesulfonamide

1-(3,4-dichlorophenyl)methanesulfonyl chloride (1.00 g, 3.85 mmol) and ammonia (1.0 M in THF, 38.5 mL, 38.5 mmol) were suspended in THF (2 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. EtOAc (50 mL) was added and the organics were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product which was used without further purification. Yield: 0.900 g (97.3 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.31 (2H, s), 6.90 (2H, s), 7.33-7.40 (1H, m), 7.59-7.70 (2H, m).

(b) Isopropyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-(3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.200 g, 0.604 mmol), EDCI (0.174 g, 0.905 mmol), HOBt (0.090 g, 0.664 mmol), (3,4-dichlorophenyl)methanesulfonamide (0.174 g, 0.724 mmol) and DIPEA (0.315 mL, 1.81 mmol) were suspended in DCM (10 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated NH_4Cl (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave Isopropyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate as a solid. Yield: 0.292 g (87 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.56-1.70 (2H, m), 1.78-1.89 (2H, m), 2.54-2.62 (1H, m), 2.65 (3H, s), 3.08-3.20 (2H, m), 4.46-4.59 (2H, m), 4.77 (2H, s), 5.02-5.14 (1H, m), 7.25-7.32 (1H, m), 7.54 (1H, s), 7.67-7.76 (1H, m), 8.33 (1H, s), 11.7 (1H, s).

MS $^m/_z$: 553 (M+1).

Example 63

Ethyl 5-cyano-6-[3-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

1-(3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid (0.200 g, 0.691 mmol), EDCI (0.199 g, 1.04 mmol), HOBt (0.103 g, 0.760 mmol), 1-(3,4-dichlorophenyl)methanesulfonamide (0.199 g, 0.830 mmol) and DIPEA (0.361 mL, 2.07 mmol) were suspended in DCM (10 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated NH_4Cl (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave ethyl 5-cyano-6-[3-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate as a solid. Yield: 0.248 g (70 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.53-3.64 (1H, m), 4.19-4.35 (4H, m), 4.38-4.48 (2H, m), 4.82 (2H, s), 7.31-7.39 (1H, m), 7.59-7.70 (2H, s), 8.31 (1H, s), 11.9 (1H, s).

MS $^m/_z$: 511 (M+1).

Example 64

Ethyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-(3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.200 g, 0.630 mmol), EDCI (0.181 g, 0.945 mmol), HOBt (0.094 g, 0.693 mmol), (3,4-dichlorophenyl)methanesulfonamide (0.182 g, 0.756 mmol) and DIPEA (0.329 mL, 1.89 mmol) were suspended in DCM (10 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated NH_4Cl (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave ethyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinateas a solid. Yield: 0.273 g (80.3 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.1 Hz), 1.57-1.70 (2H, m), 1.80-1.88 (2H, m), 2.65 (3H, s), 3.10-3.18 (2H, m), 4.31 (1H, s), 4.25 (2H, q, J = 7.1 Hz), 4.50-4.58 (2H, m), 4.76 (2H, s), 7.25-7.32 (1H, m), 7.54 (1H, s), 7.68-7.75 (1H, m), 8.35 (1H, s), 11.7 (1H, s).

MS $^{m}/_{z}$: 539 (M+1).

Example 65

Isopropyl 5-cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

(a) Sodium (4-cyanophenyl)methanesulfonate

4-(chloromethyl)benzonitrile (5.00 g, 33.0 mmol) and sodium sulfite (4.42 g, 42.9 mmol) were suspended in a 30% solution of acetone in water (100 mL) and stirred at reflux for 4 h The solution was concentrated under reduced pressure. 95% EtOH (300 mL) was added and the solution heated at 50 °C. The solution was then cooled at 0 °C and filtered to afford the crude product as a solid, which was used without further purification. Yield: 7.43 g (103 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (2H, s), 7.45-7.53 (2H, m), 7.68-7.76 (2H, m).

(b) (4-Cyanophenyl)methanesulfonyl chloride

Sodium (4-cyanophenyl)methanesulfonate (7.43 g, 33.9 mmol) was suspended in a DCM (250 mL) and stirred at 0 °C. Phosphorous pentachloride (17.7 g, 84.7 mmol) was added then the solution was warmed and stirred at room temperature for 16 h. water (100 mL) was added and stirred for 5 minutes. The layers were separated and the organics were washed with brine (2 x 100 mL), dried ($MgSO_4$) filtered and concentrated to an oil which solidified on standing and used without further purification. Yield: 7.00 g (96 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (2H, s), 7.43-7.54 (2H, m), 7.70-7.79 (2H, m).

(c) 1-(4-Cyanophenyl)methanesulfonamide

1-(4-cyanophenyl)methanesulfonyl chloride (1.00 g, 4.64 mmol) was suspended in a DCM (25 mL) and stirred at room temperature. Ammonium hydroxide (6.00 mL, 46.4 mmol) was added and the solution was stirred at room temperature for 3 h. The layers were separated and the aqueous was washed with DCM (2 x 40 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated to a solid, which was used without further purification. Yield: 0.888 g (98 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (2H, s), 6.94 (2H, s), 7.51-7.61 (2H, m), 7.82-7.92 (2H, m).

(d) Isopropyl 5-cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-(3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.200 g, 0.604 mmol), EDCI (0.174 g, 0.905 mmol), HOBt (0.090 g, 0.664 mmol), (4-cyanophenyl)methanesulfonamide (0.118 g, 0.604 mmol) and DIPEA (0.315 mL, 1.81 mmol) were suspended in DCM (10 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated NH_4Cl (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave isopropyl 5-cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate as a solid. Yield: 0.232 g (75 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.56-1.70 (2H, m), 1.80-1.89 (2H, m), 2.54-2.63 (1H, m), 2.65 (3H, s), 3.08-3.19 (2H, m), 4.49-4.58 (2H, m), 4.84 (2H, s), 5.03-5.13 (1H, m), 7.47-7.54 (2H, m), 7.88-7.94 (2H, m), 8.33 (1H, s), 11.7 (1H, s).

MS $^m/_z$: 510 (M+1).

Example 66

Ethyl 5-cyano-6-[3-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

1-(3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid (0.200 g, 0.691 mmol), EDCI (0.199 g, 1.04 mmol), HOBt (0.103 g, 0.760 mmol), (4-cyanophenyl)methanesulfonamide (0.136 g, 0.691 mmol) and DIPEA (0.361 mL, 2.07 mmol) were suspended in DCM (10 mL) at room temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc (40 mL). The combined organics were washed with saturated NH_4Cl (2 x 40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash chromatography (20 % EtOAc in Hexanes then 20 % EtOAc in Hexanes with 0.1 % AcOH) gave ethyl 5-cyano-6-[3-({[(4-

cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate as a solid. Yield: 0.235 g (73 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.51-3.64 (1H, m), 4.18-4.35 (4H, m), 4.38-4.49 (2H, m), 4.90 (2H, s), 7.53-7.61 (2H, m), 7.82-7.90 (2H, m), 8.32 (1H, s), 11.9 (1H, s).

MS $^m/_z$: 468 (M+1).

Example 67

Isopropyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

(a) 1-(4-Fluorophenyl)methanesulfonamide

Ammonia gas was bubbled through THF (50 mL) at 0 °C for 5 minutes. 1-(4-fluorophenyl)methanesulfonyl chloride (1.00 g, 4.80 mmol) was added to the reaction mixture and the system allowed to warm to r.t. Ammonia gas was bubbled through the system for 5 further minutes and the reaction mixture allowed to stir for a further 30 minutes. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (2 × 50 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford 1-(4-fluorophenyl)methanesulfonamide as a solid, which was used without further purification. Yield: 0.91 g (100 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.26 (2H, s), 6.82 (2H, s), 7.18-7.24 (2H, m), 7.38-7.42 (2H, m).

(b) Isopropyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-(3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.190 g, 0.573 mmol), 1-(4-fluorophenyl)methanesulfonamide (0.141 g, 0.745 mmol), HOBt (0.101 g, 0.745 mmol) and EDCI (0.143 g, 0.745 mmol) were suspended in DCM (4 mL) and DIPEA (0.300 ml, 1.72 mmol) added. The reaction mixture was stirred overnight at r.t and then concentrated under reduced pressure. The crude reaction mixture was dissolved in MeOH (1.5 mL) and added drop-wise to a rapidly stirring solution of $KHSO_4$ (0.380 g, 2.865 mmol) in water (20 mL). The product was collected by filtration, washed with water (3 × 10 mL) and dried under vacuum. The dry product was slurried in IPA (4 mL) and stirred and

heated at 50 °C for 1h. The compound was isolated by filtration and dried under high vacuum to give isopropyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate as a solid. Yield: 0.150 g (54 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.57-1.70 (2H, m), 1.80-1.89 (2H, m), 2.50-2.65 (1H, m), 2.65 (3H, s), 3.09-3.20 (2H, m), 4.49-4.58 (2H, m), 4.70 (2H, s), 5.04-5.12 (1H, m), 7.21-7.29 (2H, m), 7.30-7.38 (2H, m), 8.32 (1H, s), 11.62 (1H, s).
MS $^m/_z$: 503 (M+1).

Example 68

Isopropyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

(a) 1-(4-Chlorophenyl)methanesulfonamide

Ammonia gas was bubbled through THF (50 mL) at 0 °C for 5 minutes. 1-(4-fluorophenyl)methanesulfonyl chloride (1.00 g, 4.80 mmol) was added to the reaction mixture and the system allowed to warm to r.t. Ammonia gas was bubbled through the system for 5 further minutes and the reaction mixture allowed to stir for a further 30 minutes. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (2 × 50 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford 1-(4-chlorophenyl)methanesulfonamide as a solid, which was used without further purification. Yield: 0.91 g (100 %).

(b) Isopropyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

1-(3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.178 g, 0.537 mmol), (4-chlorophenyl)methanesulfonamide (0.144 g, 0.698 mmol), HOBt (0.0944 g, 0.698 mmol) and EDCI (0.134 g, 0.698 mmol) were suspended in DCM (4 mL) and DIPEA (0.476 mL, 2.69 mmol) added. The reaction mixture was stirred overnight at r.t and then concentrated under reduced pressure. The crude reaction mixture was dissolved in MeOH (1.5 mL) and added drop-wise to a rapidly stirring solution of $KHSO_4$ (0.380 g, 2.865 mmol) in water (20 mL). The product was collected by filtration, washed with water (3 × 10 mL) and dried under vacuum. The dry product was slurried in IPA (5 mL) and stirred and heated at 50 °C for 1h. The compound was isolated by filtration and dried under high

vacuum to give isopropyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate as a solid. Yield: 0.150 g (52 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.60-1.70 (2H, m), 1.80-1.89 (2H, m), 2.50-2.65 (1H, m), 2.65 (3H, s), 3.09-3.19 (2H, m), 4.50-4.58 (2H, m), 4.72 (2H, s), 5.04-5.12 (1H, m), 7.31 (2H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.4 Hz), 8.32 (1H, s), 11.63 (1H, s).

MS $^m/_z$: 519 (M+1).

Example 69

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-isopropylnicotinate

(a) 1-[3-Cyano-5-(ethoxycarbonyl)-6-isopropylpyridin-2-yl]azetidine-3-carboxylic acid

To a solution of ethyl 6-chloro-5-cyano-2-isopropylnicotinate (0.286 g, 1.13 mmol) and DIPEA (0.591 mL, 3.40 mmol) in DMF (3.0 mL) was added azetidine-3-carboxylic acid (0.132 g, 1.31 mmol) and the resulting heterogenous mixture was heated to 90 °C for 3 h. The reaction mixture was diluted with EtOAc (75 mL), washed with saturated NH_4Cl (3x50 mL), brine (50 mL), dried ($MgSO_4$) and filtered through silica gel. Concentration followed by flash chromatography (1% HOAc, 20% EtOAc, hexanes) gave 1-(3-cyano-5-(ethoxycarbonyl)-6-isopropylpyridin-2-yl)azetidine-3-carboxylic acid as a solid. Yield: 0.118 g (33 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (6H, d, J = 6.6 Hz), 1.37 (3H, t, J = 7.5 Hz), 3.60-3.68 (1H, m), 3.95-4.02 (1H, m), 4.31 (2H, q, J = 7.5 Hz), 4.57-4.65 (4H, m), 8.24 (1H, s).

MS $^m/_z$: 318 (M+1).

(b) Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-isopropylnicotinate

A solution of 1-(3-cyano-5-(ethoxycarbonyl)-6-isopropylpyridin-2-yl)azetidine-3-carboxylic acid (0.115 g, 0.362 mmol), EDCI (0.0834 g, 0.435 mmol), HOBtxH_2O (0.0666 g, 0.435 mmol), 1-phenylmethanesulfonamide (0.0620 g, 0.362 mmol) and DIPEA (0.189 mL, 1.09 mmol) in DCM (3.0 mL) was stirred at r.t for 18 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NH_4Cl (2 x 40 mL) and brine (40 mL). The

organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Flash chromatography (1 % MeOH, 1 % HOAc, DCM) gave ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-isopropylnicotinate as a solid. Yield: 0.125 g (70 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (6H, d, J = 6.6 Hz), 1.38 (3H, t, J = 6.8), 3.29-3.36 (1H, m), 3.96-4.02 (1H, m), 4.32 (2H, q, J = 6.8 Hz), 4.45-4.46 (4H, m), 4.69 (2H, s), 7.36-7.43 (5H, m), 7.56 (1H, br s), 8.24 (1H, s).
MS $^m/_z$: 471 (M+1).

Example 70

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-ethylnicotinate

(a) 1-(3-Cyano-5-(ethoxycarbonyl)-6-ethylpyridin-2-yl)azetidine-3-carboxylic acid
To a solution of ethyl 6-chloro-5-cyano-2-ethylnicotinate (0.290 g, 1.22 mmol) and DIPEA (0.635 mL, 3.65 mmol) in DMF (3.0 mL) was added azetidine-3-carboxylic acid (0.135 g, 134 mmol) and the resulting heterogenous mixture was heated to 90 °C for 3 h. The reaction mixture was diluted with EtOAc (75 mL), washed with saturated NH_4Cl (3x50 mL), brine (50 mL), dried ($MgSO_4$) and filtered through silica gel. Concentration followed by flash chromatography (1% HOAc, 20% EtOAc, hexanes) gave 1-(3-cyano-5-(ethoxycarbonyl)-6-ethylpyridin-2-yl)azetidine-3-carboxylic acid as a solid. Yield: 0.047 g 1 %).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J = 7.4 Hz), 1.37 (3H, t, J = 7.0 Hz), 3.10 (2H, q, J = 7.4 Hz), 3.60-3.68 (1H, m), 4.31 (2H, q, J = 7.4 Hz), 4.58-4.66 (4H, m), 8.27 (1H, s).
MS $^m/_z$: 304 (M+1).

(b) Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-ethylnicotinate
A solution of 1-(3-cyano-5-(ethoxycarbonyl)-6-ethylpyridin-2-yl)azetidine-3-carboxylic acid (0.0450 g, 0.148 mmol), EDCI (0.0341 g, 0.178 mmol), HOBt x.H_2O (0.0273 g, 0.178 mmol), 1-phenylmethanesulfonamide (0.0254 g, 0.148 mmol) and DIPEA (0.0775 mL, 0.445 mmol) in DCM (3.0 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NH_4Cl (2 x 40 mL) and brine (40 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Flash chromatography (1 % MeOH, 1 % HOAc, DCM) gave ethyl 6-(3-

{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-ethylnicotinate as a solid. Yield: 0.055 g (77 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J = 7.6 Hz), 1.38 (3H, t, J = 7.1 Hz), 3.11 (2H, q, J = 7.6 Hz), 3.29-3.36 (1H, m), 4.32 (2H, q, J = 7.1 Hz), 4.45-4.47 (4H, m), 4.69 (2H, s), 7.36-7.44 (5H, m), 7.57 (1H, br s), 8.28 (1H, s).

MS $^m/_z$: 457 (M+1).

Example 71

Ethyl 5-cyano-2-methyl-6-[3-({[(1-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

(a) N-(tert-Butyl)-1-phenylmethanesulfonamide

To a solution of phenylmethanesulfonyl chloride (10.6 g, 55.7 mmol) and tert-butyl amine (23.6 mL, 223 mmol) in DCM (200 mL) at 0 °C was added DIPEA (29.1 mL, 167 mmol). The reaction mixture was warmed to r.t, stirred for 16 h and then concentrated. The mixture was diluted with EtOAc (1000 mL), washed with saturated NH_4Cl (2x250 mL), saturated $NaHCO_3$ (2x250 mL), brine (50 mL), dried ($MgSO_4$) and filtered through silica gel. The crude solid was sonicated in a mixture of Et_2O (100 mL) and hexanes (50 mL) producing crystals, which were collected and washed with 1:1 Et_2O/hexanes (50 mL) and pure hexanes (50 mL). Yield: 5.32 g (44 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (9H, s), 3.93 (1H, br s), 4.24 (2H, s), 7.35-7.41 (5H, m).

(b) N-(tert-Butyl)-1-phenylethanesulfonamide

To a solution of N-(tert-butyl)-1-phenylmethanesulfonamide (0.918 g, 4.04 mmol) in THF (40 mL) cooled to -78 °C was added dropwise *tert*-butyl lithium (1.70 M in pentane, 4.75 mL, 8.08 mmol). The reaction was warmed to 0 °C for 1 h and then cooled to –78 °C. Dropwise addition of iodomethane (0.252 mL, 4.04 mmol) produced a cloudy mixture which was stirred at –78 °C for 15 minutes then 0°C for 1 h. The reaction mixture was quenched with saturated NH_4Cl (25 mL), diluted with EtOAc (75 mL), washed with saturated NH_4Cl (3x50 mL), brine (50 mL), dried ($MgSO_4$) and filtered through silica gel. Concentration followed by flash chromatography (DCM) gave N-(tert-butyl)-1-phenylethanesulfonamide as an oil. Yield: 0.900 g (92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (9H, s), 1.78 (3H, d, J = 7.3 Hz), 3.69 (1H, br s), 4.18 (1H, q, J = 7.3 Hz), 7.33-7.39 (3H, m), 7.42-7.45 (2H, m).

(c) 1-Phenylethanesulfonamide

A solution of N-(tert-butyl)-1-phenylethanesulfonamide (0.900 g, 3.73 mmol) was stirred in TFA (50 mL) for 24 h. Concentration followed by azeotropping from toluene (2 x 50 mL) produced the crude product, which was dissolved in DCM (25 mL) and passed through silica gel producing 1-phenylethanesulfonamide as a solid. Yield: 0.210 g (30 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (3H, d, J = 7.2 Hz), 4.27-4.33 (3H, m), 7.38-7.42 (3H, m), 7.45-7.48 (2H, m).

(d) Ethyl 5-cyano-2-methyl-6-[3-({[(1-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

A solution of 1-(3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid (0.0700 g, 0.242 mmol), EDCI (0.0649 g, 0.339 mmol), HOBtxH_2O (0.0519 g, 0.339 mmol), 1-phenylethanesulfonamide (0.0628 g, 0.0.339 mmol) and DIPEA (0.126 mL, 0.726 mmol) in DCM (3.0 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with saturated NH_4Cl (2 x 40 mL) and brine (40 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure to afford crude product. Flash chromatography (1 % MeOH, 1 % HOAc, DCM) gave Ethyl 5-cyano-2-methyl-6-[3-({[(1-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate as a solid. Yield: 0.105 g (95 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 1.88 (3H, d, J = 7.2 Hz), 2.72 (3H, s), 3.17-3.24 (1H, m), 4.25-4.48 (6H, m), 4.86 (1H, q, J = 7.2 Hz), 7.40-7.44 (5H, m), 8.28 (1H, s).

MS $^m/_z$: 457 (M+1).

Example 72

Propyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester (0.080 g, 0.181 mmol) and molecular sieves (4Å, 0.100 g) were dissolved in n-propanol (2 mL) and DMSO (2 mL) and stirred at r.t for 1 h. Sodium hydride (95 %, 0.014 g, 0.542 mmol) was added to the reaction mixture and stirred overnight at r.t. HCl (conc.) was

added drop-wise to the mixture until the pH was lowered to pH 2. The solid was filtered and collected. The reaction mixture was concentrated under reduced pressure. WATER (30 mL) was added and the aqueous was washed with EtOAc (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid, which was combined with the filtered solid. Flash chromatography (10 % EtOAc in hexanes with 0.1% AcOH) gave propyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinateas a solid. Yield: 0.020 g (24.2 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, t, J = 7.4 Hz), 1.74-1.82 (2H, m), 2.73 (3H, s), 3.29-3.36 (1H, m), 4.22 (2H, t, J = 6.7 Hz), 4.44-4.50 (4H, m), 4.69 (2H, s), 7.35-7.45 (5H, m) 8.29 (1H, s).

MS $^m/_z$: 457 (M+1).

Example 73

Isobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester (0.080 g, 0.181 mmol) and molecular sieves (4Å, 0.100 g) were dissolved in iso-butanol (2 mL) and DMSO (2 mL) and stirred at r.t for 1 h. Sodium hydride (95%, 0.014 g, 0.542 mmol) was added to the reaction mixture and stirred for 4 h at r.t. EtOAc (30 mL) was added and the reaction mixture was filtered through celite. HCl (conc.) was added drop-wise to the mixture until the pH was lowered to pH 2. The reaction mixture was concentrated under reduced pressure. Water (30 mL) was added and the aqueous was washed with EtOAc (3 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a solid. Flash chromatography (10% EtOAc in hexanes with 0.1% AcOH) gave Isobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.040 g (47.0 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (6H, d, J = 6.7 Hz), 2.02-2.10 (1H, m), 2.73 (3H, s), 3.30-3.37 (1H, m), 4.05 (2H, d, J = 6.6 Hz), 4.42-4.50 (4H, m), 4.69 (2H, s), 7.36-7.44 (5H, m), 8.28 (1H, s).

MS $^m/_z$: 471 (M+1).

Example 74

Isopropyl 5-cyano-2-methyl-6-{4-[({[4-(trifluoromethyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

(a) 1-[4-(Trifluoromethyl)phenyl]methanesulfonamide

1-(4-(Trifluoromethyl)phenyl)methanesulfonyl chloride (1.00 g, 3.87 mmol) and ammonia (1.0 M in THF, 38.7 mL, 38.7 mmol) were suspended in THF (2 mL) and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure. EtOAc (50 mL) was added and the organics were washed with saturated $NaHCO_3$ (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford 1-(4-(trifluoromethyl)phenyl)methanesulfonamide which was used without further purification. Yield: 0.900 g (97.3 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (2H, s), 6.94 (2H, s), 7.60 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz).

(b) Isopropyl 5-cyano-2-methyl-6-{4-[({[4-(trifluoromethyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

1-(3-Cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.200 g, 0.604 mmol), EDCI (0.174 g, 0.905 mmol), 1-(4-(trifluoromethyl)phenyl)methanesulfonamide (0.173 g, 0.724 mmol), HOBt (0.090 g, 0.664 mmol) and DIPEA (0.315 mL, 1.81 mmol) were suspended in DCM (10 mL) and then refluxed for 3 h. The reaction mixture was cooled to r.t and concentrated under reduced pressure. The crude reaction mixture was dissolved in IPA (10 mL) and added drop-wise to a rapidly stirring solution of $KHSO_4$ (0.411 g, 3.02 mmol) in water (100 mL). The product was collected by filtration, washed with water (3 × 20 mL) and dried under vacuum. The dry product was purified by preparing a slurry in IPA (100 mL) and stirring and heating at 50 °C for 1 h. The product was isolated by filtration and dried under high vacuum to give isopropyl isopropyl 5-cyano-2-methyl-6-{4-[({[4-(trifluoromethyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate. Yield: 0.173 g (52.0 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (6H, d, J = 6.2 Hz), 1.77-1.97 (4H, m), 2.41-2.51 (1H, m), 2.73 (3H, s), 3.09-3.20 (2H, m), 4.62-4.71 (2H, m), 4.75 (2H, s), 5.15-5.25 (1H, m), 7.50 (2H, d, J = 8.0 Hz), 7.56 (1H, s), 7.67 (2H, d, J = 8.0 Hz), 8.34 (1H, s). MS $^m/_z$: 553 (M+1).

Example 75

Isopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

1-(4-methylphenyl)methanesulfonamide (0.099 g, 0.534 mmol) dissolved in DCM (2 mL) and DIPEA (0.155 g, 1.2 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.124 g, 0.374 mmol) and TBTU (0.213 g, 0.663 mmol) in DCM (2 mL) and the reaction was stirred at r.t for 15 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was dried ($MgSO_4$), filtered and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.103 g (55 %).

1H NMR (500 MHz, DMSO-d_6): 1.31 (6H, d), 1.64 (2H, m), 1.84 (2H, m), 2.31 (3H, s), 2.58 (1H, m), 2.65 (3H, s), 3.13 (2H, m), 4.54 (2H, m), 4.64 (2H,s), 5.08 (1H, m), 7.16-7.23 (4H, dd), 8.33 (1H, s), 11.56 (1H, s).

MS $^m/_z$: 499 (M+1)

Example 76

Isopropyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

TBTU (0.100 g, 0.311 mmol) and and DIPEA (0.074 g, 0.574 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.104 g, 0.314 mmol) in DCM (2 mL)and the reaction was stirred at r.t for 40 minutes. 1-(3-methylphenyl)methanesulfonamide (0.071 g, 0.383 mmol) was added together with DCM (2 mL) and the stirring was continued for 18 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was filtered through a phase separator and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.119 g (76 %).

1H NMR (500 MHz, DMSO-d_6): 1.31 (6H, d), 1.64 (2H, m), 1.82 (2H, m), 2.31 (3H, s), 2.58 (1H, m), 2.65 (3H, s), 3.14 (2H, m), 4.54 (2H, m), 4.65 (2H,s), 5.08 (1H, m), 7.08-7.31 (4H, m), 8.33 (1H, s), 11.58 (1H, s).

MS $^m/_z$: 499 (M+1)

Example 77

Isopropyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

TBTU (0.097 g, 0.302 mmol) and and DIPEA (0.074 g, 0.574 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.100 g, 0.302 mmol) in DCM (2 mL)and the mixture was stirred at r.t for 2.5 h. 1-(3-fluorophenyl)methanesulfonamide (0.074 g, 0.360 mmol) was added together with DCM (2 mL) and the stirring was continued for 18 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was filtered through a phase separator and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.115 g (76 %).
1H NMR (500 MHz, DMSO-d_6): 1.31 (6H, d), 1.63 (2H, m), 1.83 (2H, m), 2.59 (1H, m), 2.65 (3H, s), 3.14 (2H, m), 4.54 (2H, m), 4.75 (2H,s), 5.08 (1H, m), 7.12-7.47 (4H, m), 8.32 (1H, s), 11.68 (1H, s).
MS $^m/_z$: 503 (M+1)

Example 78

Isopropyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

TBTU (0.097 g, 0.302 mmol) and and DIPEA (0.074 g, 0.574 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.100 g, 0.302 mmol) in DCM (2 mL)and the mixture was stirred at r.t for 2.5 h. The mixture was added to 1-(2-fluorophenyl)methanesulfonamide (0.068 g, 0.360 mmol) in DCM (2 mL) and the stirring was continued for 18 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was filtered through a phase separator and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.115 g (76 %).
1H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.64 (2H, m), 1.87 (2H, m), 2.61 (1H, m), 2.64 (3H, s), 3.15 (2H, m), 4.53 (2H, m), 4.75 (2H, s), 5.07 (1H, m), 7.24-7.47 (4H, m), 8.31 (1H, s), 11.74 (1H, s).

MS $^m/_z$: 503 (M+1).

Example 79

Isopropyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

TBTU (0.097 g, 0.302 mmol) and and DIPEA (0.074 g, 0.574 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.100 g, 0.302 mmol) in DCM (2 mL)and the mixture was stirred at r.t for 2.5 h. The mixture was added to 1-(3-chlorophenyl)methanesulfonamide (0.074 g, 0.360 mmol) in DCM (2 mL) and the stirring was continued for 18 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was filtered through a phase separator and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.118 g (75 %).

1H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.62 (2H, m), 1.82 (2H, m), 2.58 (1H, m), 2.63 (3H, s), 3.13 (2H, m), 4.52 (2H, m), 4.74 (2H, s), 5.07 (1H, m), 7.24-7.47 (4H, m), 8.31 (1H, s), 11.66 (1H, s).

MS $^m/_z$: 520 (M+1)

Example 80

Isopropyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

TBTU (0.097 g, 0.302 mmol) and and DIPEA (0.074 g, 0.574 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.100 g, 0.302 mmol) in DCM (2 mL)and the mixture was stirred at r.t for 2.5 h. The mixture was added to 1-(2-chlorophenyl)methanesulfonamide (0.074 g, 0.360 mmol) in DCM (2 mL) and the stirring was continued for 18 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was filtered through a phase separator and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.116 g (74 %).

1H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.65 (2H, m), 1.89 (2H, m), 2.63 (1H, m), 2.63 (3H, s), 3.15 (2H, m), 4.53 (2H, m), 4.85 (2H, s), 5.07 (1H, m), 7.38-7.54 (4H, m), 8.31 (1H, s), 11.80 (1H, s).

MS $^m/_z$: 520 (M+1)

Example 81

Ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

and sodium ({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)[(4-methylbenzyl)sulfonyl]azanide

TBTU (1.162 g, 3.62 mmol) and and DIPEA (2.04 g, 15.76 mmol) was added to a solution of 1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.100 g, 0.302 mmol) in DCM (53 mL) and the mixture was stirred at r.t for 5 minutes. 1-(4-methylphenyl)methanesulfonamide (0.67 g, 3.62 mmol) was added and the stirring was continued over night. The reaction mixture was concentrated and partioned between EtOAc (200 mL), water (50 mL) and formic acid (5 mL). The organic phase was separated and evaporated to give a crude pink colored solid which was purified by preparative HPLC (Kromasil C8 a gradient of 0.1 M NH_4OAc and CH_3CN) to give ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate as an off white solid. Yield: 0.687 g (45 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.56 - 1.68 (2H, m), 1.79 - 1.87 (2H, m), 2.29 (3H, s), 2.41-2.60 (1H, m, concealed under the DMSO-peak), 2.64 (3H, s), 3.09 - 3.18 (2H, m), 3.29 (1H, s), 4.24 (2H, q, J = 7.1 Hz), 4.48 - 4.56 (2H, m), 4.59 (2H, s), 7.13 - 7.21 (4H, m), 8.33 (1H, s)

MS $^m/_z$: 485 (M+1).

Ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate (0.687 g, 1.38 mmol) was dissolved in CH_3CN /water and 1 M NaOH (1.38 mL) was added and the mixture was freeze dried to give

Sodium ({1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidin-4-yl}carbonyl)[(4-methylbenzyl)sulfonyl]azanide as a whithe solid. Yield: 0.726 g (104 %, conatining some residual water).

1H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.51 - 1.65 (2H, m), 1.74 - 1.82 (2H, m), 2.17 - 2.23 (1H, m), 2.25 (3H, s), 2.63 (3H, s), 3.14 - 3.25 (2H, m), 4.17 (2H, s), 4.24

(2H, q, J = 7.1 Hz), 4.37 - 4.45 (2H, m), 7.03 (2H, d, J = 8.1 Hz), 7.10 (2H, d, J = 8.1 Hz), 8.30 (1H, s)

Example 82

Ethyl 5-cyano-6-{4-[({[2-(methoxycarbonyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}-2-methylnicotinate

Prepared according to method B starting from methyl 2-[(aminosulfonyl)methyl]benzoate.Yield=77 mg (69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ?1.30 (3H, t, *J* = 7.1 Hz), 1.56 - 1.71 (2H, m), 1.81 - 1.89 (2H, m), 2.48 - 2.53 (1H, m), 2.65 (3H, s), 3.08 - 3.20 (2H, m), 3.83 (3H, s), 4.25 (2H, q, *J* = 7.1 Hz), 4.46 - 4.61 (2H, m), 5.14 (2H, s), 7.35 (1H, d, *J* = 7.5 Hz), 7.46 - 7.68 (2H, m), 7.85 (1H, d, *J* = 7.9 Hz), 8.34 (1H, s), 11.58 - 11.66 (1H, m)

MS $^m/_z$: 529 (M+1).

Example 83

Ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-(3-fluorophenyl)methanesulfonamide.Yield=76 mg (74%).

1H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.69 (2H, m), 1.78 - 1.87 (2H, m), 2.41-2.60 (1H, m, concealed under DMSO-peak), 2.65 (3H, s), 3.10 - 3.20 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.52 (2H, d, J = 13.3 Hz), 4.72 (2H, s), 7.08 - 7.16 (2H, m), 7.19 - 7.29 (1H, m), 7.45 (1H, q, J = 7.4 Hz), 8.34 (1H, s), 11.67 (1H, s)

MS $^m/_z$: 489 (M+1).

Example 84

Isopropyl 5-cyano-2-methyl-6-[4-({[2-(2-methylphenyl)ethyl]sulfonyl}carbamoyl)piperidin-1-yl]nicotinate

TBTU (0.097 g, 0.302 mmol) and and DIPEA (0.074 g, 0.574 mmol) was added to a solution of 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.100 g, 0.302 mmol) in DCM (2 mL)and the mixture was stirred at r.t for 2.5 h. The mixture was added to 2-(2-methylphenyl)ethanesulfonamide (0.074 g, 0.360 mmol) in DCM (2 mL) and the stirring was continued for 18 h. $NaHCO_3$ (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was filtered through a phase

separator and evaporated to give a crude product. Purification by preparative HPLC (Kromasil C8, 21.5 x 100 mm column, flow 25 mL/minute using a gradient of 0.1 M NH_4OAc and CH_3CN) gave the pure product as a solid. Yield: 0.098 g (63 %).

1H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.59 (2H, m), 1.89 (2H, m), 2.24 (3H, s), 2.63 (1H, m), 2.63 (3H, s), 2.95 (2H, m), 3.15 (2H, m), 3.59 (2H, m), 4.52 (2H, m), 5.07 (1H, m), 7.11-7.18 (4H, m), 8.30 (1H, s), 11.80 (1H, s).

MS $^m/_z$: 513 (M+1), 511 (M-1).

Example 85

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

(a) Ethyl 5-acetyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

Ethyl 5-acetyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate was prepared from 3-oxobutanamide employing the same methodology that produced ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate.

(b) Ethyl 5-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

To a solution of H_2O_2 (30 % in water, 74.8 mL, 792 mmol) in EtOH (500 mL) cooled to 0°C was added drop-wise TFA (89.5 mL, 1.16 mol). A suspension of ethyl 5-acetyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (11.8 g, 52.8 mmol) in EtOH (500 mL) was added slowly to the reaction mixture, which was then heated to reflux for 24 h and then allowed to cool to r.t. In a separate flask, TFA (89.5 mL, 1.16 mol) was added drop-wise to a solution of H_2O_2 (30 % in water, 74.8 mL, 792 mmol) in EtOH (100 mL) cooled to 0°C and stirred for 15 minutes. This solution was then added to the reaction mixture, which was heated to reflux for an additional 18 h. After cooling to r.t, the mixture was concentrated under reduced pressure and azeotroped from toluene (8 x 100 mL). Addition of CH_3CN (100 mL) produced a solid which was collected and washed CH_3CN (100 mL). Yield: 2.50 g (24 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ δ 1.37 (3H, t, J = 7.1 Hz), 2.66 (3H, s), 4.31 (2H, q, J = 7.1 Hz), 6.35 (1H, br s), 7.50 (1H, s), 11.75 (1H, br s).

MS $^m/_z$: 196 (M-1).

(c) Ethyl 5-(4-methoxy-4-oxobutoxy)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

To a solution of ethyl 5-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (0.824 g, 4.18 mmol) in DMF (25 mL) cooled to 0°C was added LiH (0.0385 g, 4.60 mmol) and the resulting mixture was stirred for 1.5 h. Methyl 4-bromobutanoate (0.832 g 4.60 mmol) and TBAI (0.005 g, 0.0135 mmol) were added and the reaction was heated to 60 °C for 20 h. After cooling to r.t the mixture was diluted with EtOAc (200 mL), washed with saturated NH_4Cl (3 x 100 mL), brine, dried ($MgSO_4$) and passed through silica gel. Flash chromatography (1:1 EtOAc/hexanes) furnished ethyl 5-(4-methoxy-4-oxobutoxy)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate as a solid. Yield: 0.60g (48 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J = 7.1 Hz), 2.15-2.22 (2H, m), 2.60 (2H, t , J = 7.1 Hz), 2.73 (3H, s), 3.71 (3H, s), 4.13 (2H, t, J = 6.0 Hz), 4.39 (2H, q, J = 7.1 Hz), 7.70 (1H, s).

MS $^m/_z$: 298 (M+1).

(d) Ethyl 6-chloro-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

A suspension of ethyl 5-(4-methoxy-4-oxobutoxy)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (0.600 g, 2.02 mmol) in $POCl_3$ (25 mL) was heated to 60 °C for 5 h. After cooling to r.t, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (200 mL), washed with saturated $NaHCO_3$ (2 x 100 mL), brine, dried ($MgSO_4$) and passed through silica gel. Concentration afforded ethyl 6-chloro-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate. Yield: 0.589 g (92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J = 7.1 Hz), 2.15-2.22 (2H, m), 2.60 (2H, t , J = 7.1 Hz), 2.74 (3H, s), 3.71 (3H, s), 4.13 (2H, t, J = 6.0 Hz), 4.39 (2H, q, J = 7.1 Hz), 7.70 (1H, s).

MS $^m/_z$: 316 (M+1).

(e) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

A suspension of ethyl 6-chloro-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate (0.300 g, 1.23 mmol), N-(benzylsulfonyl)piperidine-4-carboxamide hydrochloride (0.413 g, 1.30 mmol) and DIPEA (0.371 mL, 2.13 mmol) in NMP (2 mL) was stirred at 80°C for 24 h. The reaction mixture was cooled to r.t and poured into EtOAc (60 mL) and saturated NH_4Cl (30 mL). The organics were washed with water (3 x 50 mL), brine (1 x 50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude material. Flash

chromatography (1:4 EtOAc / hexanes with 1 % AcOH) furnished ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate as a solid. Yield: 0.060 g (29 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 1.78-1.84 (4H, m), 2.11-2.17 (2H, m), 2.32-2.40 (1H, m), 2.52 (2H, t, J = 7.2 Hz), 2.65 (3H, s), 2.80-2.87 (2H, m), 3.68 (3H, s), 4.01 (2H, t, J = 6.2 Hz), 4.29-4.36 (4H, m), 4.68 (2H, s), 7.35-7.40 (5H, m), 7.54 (1H, s).

MS $^m/_z$: 562 (M+1).

Example 86

4-{[2-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid

A solution of ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate (0.050 g, 0.089 mmol) in THF (4 mL) was cooled to 0°C and treated with NaOH (1.00 M, 0.18 mL, 0.18 mmol). The reaction was warmed to r.t and stirred for 18 h. After dilution with EtOAc (100 mL), the mixture was washed with saturated NH_4Cl (2 x 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (50 % EtOAc/hexanes with 1 % HOAc) furnished 4-(2-(4-(benzylsulfonylcarbamoyl)piperidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yloxy)butanoic acid as a solid. Yield: 0.036 g (67 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 1.82-1.86 (4H, m), 2.06-2.13 (2H, m), 2.39-2.45 (1H, m), 2.50 (2H, t, J = 6.9 Hz), 2.65 (3H, s), 2.77-2.84 (2H, m), 4.02 (2H, t, J = 6.6 Hz), 4.24-4.27 (2H, m), 4.32 (2H, q, J = 7.1 Hz), 4.68 (2H, s), 7.36-7.40 (5H, m), 7.59 (1H, s).

MS $^m/_z$: 548 (M+1).

Example 87

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

(a) 1-[5-(ethoxycarbonyl)-3-(4-methoxy-4-oxobutoxy)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid

Azetidine-3-carboxylic acid (0.380 g, 3.76 mmol) and tetrabutylammonium hydroxide (2.3 g, 3.55 mmol, as a 40% solution in water) were combined in MeOH. The azetidine acid was

dissolved and the solution was then concentrated *in vacuo* and azeotroped with toluene twice. The resulting oil was pumped under vacuum. NMP (9 mL) was added along with dried 4A molecular sieves. The resulting solution was used as a 0.35 M solution of tetrabutylammonium azetidine-3-carboxylate. Ethyl 6-chloro-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate (0.060 g, 0.19 mmol) was dissolved in an NMP solution of tetrabutylammonium azetidine-3-carboxylate (2.0 mL, 0.70 mmol). The reaction was stirred at room temperature. After 2 hr the reaction was complete and was poured into EtOAc (75 mL), washed with NH_4Cl (2 x 40 mL) and dried ($MgSO_4$). The solution was concentrated *in vacuo* to provide the product, 1-[5-(ethoxycarbonyl)-3-(4-methoxy-4-oxobutoxy)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid, which was used without further purification. Yield 0.070 g (97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.08-2.15 (2H, m), 2.51 (2H, t, J = 7.3 Hz), 2.63 (3H, s), 3.52-3.59 (1H, m), 3.70 (3H, s), 3.96 (2H, t, J = 6.1 Hz), 4.31 (2H, q, J = 7.1 Hz), 4.22-4.44 (4H, m), 7.40 (1H, s).

MS $^m/_z$: 379 (M-1).

(b) Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

1-(5-(Ethoxycarbonyl)-3-(4-methoxy-4-oxobutoxy)-6-methylpyridin-2-yl)azetidine-3-carboxylic acid (0.070 g, 0.18 mmol), HOBt (0.032 g, 0.24 mmol), 1-phenylmethanesulfonamide (0.044 g, 0.26 mmol) and EDCI (0.046 g, 0.24 mmol) were partially dissolved in dry DCM (2.5 mL) and then DIPEA (0.16 mL, 0.92 mmol) was added. The reaction was allowed to stir overnight at r.t. The reaction was then concentrated with vacuum and the residue was dissolved in MeOH (0.5 mL). The resulting solution was added slowly to a solution of $KHSO_4$ (0.125 g, 0.92 mmol) in water (7 mL). No clear precipitate formed so the mixture was partitioned between EtOAc (40 m) and water (10 mL). The organic phase was washed with saturated NH4Cl then brine and dried ($MgSO_4$). The solution was concentrated *in vacuo* and purified by column chromatography (30% EtOAc/hexanes to 50% EtOAc/hexanes then 0.1% HOAc added) to provide ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate as an oil. Yield: 0.032 g (33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.06-2.13 (2H, m), 2.48 (2H, t, J = 7.3 Hz), 2.62 (3H, s), 3.29-3.36 (1H, m), 3.67 (3H, s), 3.96 (2H, t, J = 6.1 Hz), 4.28-4.34 (6H, m), 4.67 (2H, s), 7.37-7.38 (5H, m), 7.41 (1H, s).

MS $^m/_z$: 534 (M+1).

Example 88

Ethyl 6-(4-{[(anilinosulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

1-(3-Cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)piperidine-4-carboxylic acid (0.155 g, 0.488 mmol) was partially dissolved in dry DCE (4 mL). CDI (0.103 g, 0.635 mmol) was added and the reaction mixture was heated at 50 °C for 3 hours. N-Phenylsulfamide [*Bioorganic & Medicinal Chemistry Letters* **2003**, 18, 837] (0.101 g, 0.586 mmol) was added followed by DBU (0.0875 mL, 0.586 mmol) and the reaction was heated at 50 °C for an additional 16 hours. The reaction was cooled and concentrated. The residue was partitioned between EtOAc (75 mL) and aqueous NH_4Cl (50 mL) and the organic phase was further washed with NH_4Cl (40 mL) and brine (40 mL). The solution was then concentrated to provide a white solid which was triturated with MeOH to provide the desired product, ethyl 6-(4-{[(anilinosulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate, as a white solid. Yield 0.16 g (70%).

NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 1.36-1.46 (2H, m), 1.63-1.65 (2H, m), 2.45-2.50 (1H, obs), 2.62 (3H, s), 3.09 (2H, d, J = 11.6 Hz), 4.24 (2H, q, J = 7.1 Hz), 4..36-4.39 (2H, m), 7.10 (1H, t, J = 7.4 Hz), 7.15 (2H, d, J = 7.7 Hz), 7.31 (2H, t, J = 7.9 Hz), 8.31 (1H, s), 10.38 (1H, s), 11.73 (1H, s).

MS $^m/_z$: 472 (M+1).

Example 89

Ethyl 5-cyano-2-methyl-6-{4-[({[methyl(phenyl)amino]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

Ethyl 5-cyano-2-methyl-6-(4-(N-phenylsulfamoylcarbamoyl)piperidin-1-yl)nicotinate (0.047 g, 0.10 mmol) was dissolved in dry DMF (1 mL) and cooled to 0 °C. Sodium hydride (0.010 g, 60% w/w, 0.25 mmol) was added and the reaction was warmed to room temperature and then at 35 °C for 5 minutes. The reaction was returned to 0 °C and then iodomethane (6.0 μL, 0.010 mmol) was added. After 30 minutes, the reaction was warmed to room temperature and

stirred for 2 hours. The reaction was then acidified with HOAc (0.2 mL) and partitioned between EtOAc (75 mL) and aqueous NH_4Cl (50 mL). The organic phase was washed with NH_4Cl (30 mL), water (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (30 to 40 % EtOAc/hexanes) to provide the desired product, ethyl 5-cyano-2-methyl-6-(4-(N-methyl-N-phenylsulfamoylcarbamoyl)piperidin-1-yl)nicotinate. Yield: 0.012 g (25%).

NMR spectroscopy using NOE confirmed the desired regioisomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 1.71-1.86 (4H, m), 2.35-2.42 (1H, m), 2.72 (3H, s), 3.09-3.16 (2H, m), 3.52 (3H, s), 4.32 (2H, q, J = 7.1 Hz), 4.63-4.67 (2H, m), 7.31-7.41 (5H, m), 8.35 (1H, s).

MS $^m/_z$: 486 (M+1).

Example 90

Isopropyl 5-cyano-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to method C starting from 1-(4-methylphenyl)methanesulfonamide.Yield=4 mg.(4%)

MS $^m/_z$: 471 (M+1)

Example 91

Isopropyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method C starting from 1-(3-fluorophenyl)methanesulfonamide.Yield=6.4 mg.(4.5%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 3.51-3.61 (m, 1H), 4.26-4.34 (m, 2H), 4.38-4.47 (m, 2H), 4.75-4.81 (br s, 2H), 5.04-5.12 (m, 1H), 7.16-7.28 (m, 3H), 7.39-7.48 (m, 1H), 8.30 (s, 1H), 11.88-11.94 (br s, 1H).

MS $^m/_z$: 475 (M+1)

Example 92

Isopropyl 5-cyano-2-methyl-6-[3-({[(2-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to method C starting from 2-phenylethanesulfonamide.Yield=31 mg.(22%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (d, J = 6.3 Hz, 6H), 2.63 (s, 3H), 3.00-3.07 (m, 2H), 3.52-3.61 (m, 1H), 3.70-3.77 (m, 2H), 4.24-4.32 (m, 2H), 4.38-4.47 (m, 2H), 5.04-5.12 (m, 1H), 7.20-7.35 (m, 5H), 8.29 (s, 1H), 11.88-12.03 (br s, 1H).

MS $^m/_z$: 471 (M+1)

Example 93

Isopropyl 5-cyano-6-[3-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method C starting from 1-cyclopentylmethanesulfonamide.Yield=28 mg.(21%)

^{1}H NMR (400 MHz, DMSO-d_6): δ1.24-1.34 (m, 8H), 1.48-1.66 (m, 4H), 1.82-1.92 (m, 2H), 2.17-2.27 (m, 1H), 2.64 (s, 3H), 3.46 (d, J = 6.8 Hz, 2H), 3.57-3.67 (m, 1H), 4.32-4.39 (m, 2H), 4.42-4.51 (m, 2H), 5.04-5.13 (m, 1H), 8.29 (s, 1H), 11.91 (br s, 1H).

MS $^m/_z$: 449 (M+1)

Example 94

Isopropyl 5-cyano-6-{3-[({[2-(methoxycarbonyl)benzyl]sulfonyl}amino)carbonyl]azetidin-1-yl}-2-methylnicotinate

Prepared according to method C starting from methyl 2-[(aminosulfonyl)methyl]benzoate.Yield=46 mg.(30%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 3.50-3.60 (m, 1H), 3.83 (s, 3H), 4.29-4.36 (m, 2H), 4.38-4.47 (m, 2H), 5.03-5.14 (m, 1H), 5.22 (s, 2H), 7.45-7.48 (m, 1H), 7.52-7.58 (m, 1H), 7.59-7.65 (m, 1H), 7.83-7.87 (m, 1H), 8.31 (s, 1H), 11.83-11.87 (br s, 1H).

MS $^m/_z$: (M+1)

Example 95

Isopropyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method C starting from 1-(2-fluorophenyl)methanesulfonamide.Yield=53 mg.(37%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.66 (s, 3H), 3.57-3.66 (m, 1H), 3.33-4.41 (m, 2H), 4.42-4.52 (m, 2H), 4.83 (s, 2H), 5.03-5.14 (m, 1H), 7.24-7.31 (m, 2H), 7.45-7.53 (m, 2H), 8.31 (s, 1H), 11.99 (br s, 1H).

MS $^m/_z$: 515 (M+1)

Example 96

Isopropyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate

Prepared according to method C starting from 1-(4-chlorophenyl)methanesulfonamide

Yield=76 mg.(52%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.66 (s, 3H), 3.51-3.61 (s, 1H), 4.28-4.36 (m, 2H), 4.38-4.47 (m, 2H), 4.75 (s, 2H), 5.04-5.13 (m, 1H), 7.35-7.40 (m, 2H), 7.43-7.48 (m, 2H), 8.31 (s, 1H), 11.87 (br s, 1H).

MS $^m/_z$: 491 (M+1)

Example 97

Isopropyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method C starting from 1-(4-fluorophenyl)methanesulfonamide

Yield=19 mg.(13%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 3.51-3.61 (m, 1H), 4.27-4.35 (m, 2H), 4.38-4.48 (m, 2H), 4.76 (br s, 2H), 5.04-5.13 (m, 1H), 7.14-7.26 (m, 2H), 7.37-7.48 (m, 2H), 8.31 (s, 1H), 11.81 (br s, 1H).

MS $^m/_z$: 475 (M+1)

Example 98

Isopropyl 5-cyano-6-[3-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method C starting from 1-(4-cyanophenyl)methanesulfonamide

Yield=39 mg.(27%)

^{1}H NMR (400 MHz, DMSO-d_6/CD_3OD 9:1): δ 1.31 (6H, d, J = 6.3 H), 2.65 (3H s), 3.54-3.63 (1H, m), 4.28-4.35 (2H, m), 4.39-4.48 (2H, m), 4.77 (2H, s), 5.03-5.14 (1H, m), 7.19-7.25 (2H, m), 7.38-7.44 (2H, m), 8.30 (1H, s).
MS $^m/_z$: 482 (M+1)

Example 99

Methyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

(a) 5-Cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid
KOH (1.43 g, 25.5 mmol) dissolved in EtOH (25 mL, 95%) was added to ethyl 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.69 g, 8.2 mmol) in EtOH(30 mL) to give a thick slurry which was heated to reflux (90 degrees in the oil bath) for 12 hours. The mixture was concentrated and 2 M HCl was added. The precipitate formed was filtered, washed with water and dried to give 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid as a white solid. Yield: 1.425 g (98%).
1H NMR (500MHz, DMSO-d_6): keto-form: 2.61 (3H, s), 8.40 (1H, s), 12.91 (1H, br s). ~86% and enol-form: 2.36 (3H, s), 8.09 (1H, s), 10.50 (1H, br s). ~14%
MS $^m/_z$: 179(M+1), 177(M-1).

(b) 6-Chloro-5-cyano-2-methylnicotinoyl chloride
Oxalylchloride (3.38 mL, 40 mmol) was added dropwise to a cold (ice/water bath) suspension of 5-cyano-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (0.710 g, 3.99 mmol) in dry DCM (25 mL) followed by dry DMF (0.1 mL).The reaction was stirred for 20 minutes at 0 degrees and then at room temperatrure for 30 minutes followed by reflux for 16 hours. The mixture was evaporated and the remaining black residue was co-evaporated with dry DCM (two times). The crude product was used in the next step without further purification.

(c) Methyl 6-chloro-5-cyano-2-methylnicotinate
DIPEA (0.35 mL, 2.0 mmol) was added to a solution of crude 6-chloro-5-cyano-2-methylnicotinoyl chloride (0.222 g, 1.03 mmol) in Methanol (4 mL). The reaction was stirred at r.t for 1 hour. The recation mixture was used directly in the next step without isolation.

(d) 1-[3-Cyano-5-(methoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid

Piperidine-4-carboxylic acid (0.136 g, 1.05 mmol) was added to the solution from above (assuming 100 % conversion, 0.210 g, 1 mmol) and the mixture was heated to 120 degrees in a single node microwave owen for 5 minutes. NH_4Cl(aq) was added and the reaction was extracted with DCM (3 times). The combined organic layer was separated dried and evaporated. Purification by preparative HPLC (Kromasil C8, 21.5 x 250 mm column, flow 25 mL/min using a gradient of 0.1 M NH4OAc and CH3CN) gave 0.181 g of 1-[3-cyano-5-(methoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid. Yield (60 % over three steps).

1H NMR (500MHz, DMSO-d_6): 1.54-1.63 (2H, m), 1.85-1.92 (2H, m), 2.39-2.47 (1H, m), 2.62 (3H, s), 3.22-3.29 (2H, m), 3.77 (3H, s), 4.38-4.44 (2H, m), 8.30 (1H, s).

(e) Methyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

TBTU (0.106 g, 0.33 mmol) was added to a solution of 1-[3-cyano-5-(methoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (0.090 g, 0.297 mmol) and DIPEA (0.2 mL, 1.15 mmol) in DCM (4 mL). Phenylmethanesulfonamide (0.060 g, 0.409 mmol) was added after 30 minutes and the reaction was stirred for 20 hours at r.t.. $NaHCO_3$(aq) was added and the mixture was extracted with DCM(3 times). The combined organic layer was dried and evaporated to give a crude product which was purified by reverse phase HPLC (Kromasil C8, 21.5 x 250 mm column, flow 25 mL/min using a gradient of 0.1 M NH_4OAc and CH_3CN) to give methyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate as a powder. Yield: 0.040 g (29%).

1H NMR (500MHz, DMSO-d_6): 1.58-1.68 (2H, m), 1.80-1.87 (2H, m) 2.54-2.61 (1H, m), 2.64 (3H, s), 3.13 (2H, apparent t), 3.78 (3H, s), 4.53 (2H, apparent d), 4.68 (2H,s), 7.26-7.31 (2H, m), 7.36-7.42 (3H, m), 8.32 (1H, s), 11.60 (1H, bs).

Example 100

Methyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared in the same way as descibed in Example 99 by replacing phenylmethanesulfonamide for 1-(4-methylphenyl)methanesulfonamide. Yield: 0.034 g (24 %).

1H NMR (500MHz, DMSO-d_6): 1.58-1.63 (2H, m), 1.80-1.87 (2H, m), 2.30 (3H, s), 2.53-2.62 (1H, m), 2.64 (3H, s), 3.13 (2H, apparent), 3.78 (3H s), 4.53 (2H, apparent d), 4.63 (2H, s), 7.14-7.22 (4H, m), 8.33 (1H, s), 11.55 (1H, bs).

Example 101

S-Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylpyridine-3-carbothioate

(a) S-Ethyl 6-chloro-5-cyano-2-methylpyridine-3-carbothioate

A solution of EtSH (0.22 mL, 3.0 mmol) and DIPEA (1 mL, 5.74 mmol) in THF (5 mL was added dropwise to a cold (0 degrees ice/water bath) solution of 6-chloro-5-cyano-2-methylnicotinoyl chloride (0.60 g, 2.29 mmol, See Example 99 above). The reaction was stirred at 0 degrees for 10 minutes followed by r.t. for 50 minutes. The mixture was evaporated and the residue was co-evaporated with THF(3 times) to give S-ethyl 6-chloro-5-cyano-2-methylpyridine-3-carbothioate which was used in the next step without further purification. Yield: 0.671 g (100 %).

(b) 1-{3-Cyano-5-[(ethylthio)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid

A mixture of piperidine-4-carboxylic acid (0.362 g, 2.80 mmol), S-ethyl 6-chloro-5-cyano-2-methylpyridine-3-carbothioate (0.674 g, 2.80 mmol) and DIPEA (0.5 mL, 2.87 mmol) in DMF (10 mL) was hetaed at 100 degrees for 5 minutes using a single node microwave owen. NH4Cl(aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was dried and evaporated to give a crude product which was purified by reverse phase HPLC (Kromasil C8, 21.5 x 250 mm column, flow 25 mL/min using a gradient of 0.1 M NH_4OAc and CH_3CN) to give 1-{3-cyano-5-[(ethylthio)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid. Yield: 0.453 g (48 % over three steps).

1H NMR (500MHz, DMSO-d_6): 1.27 (3h, t, J= 7.3 Hz), 1.56-1.65 (2H, m), 1.92-1.98 (2H, m), 2.28 (3H, s), 2.57-2.64 (1H, m), 2.98 (2H, q, J= 7.3 Hz), 3.24-3.28 (2H, m), 4.42-4.48 (2H, m), 8.28 (1H, s), 12.31 (1H, bs).

(c) S-Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylpyridine-3-carbothioate

TBTU (0.104 g, 0.324 mmol) and DIPEA (0.1 mL, 0.574 mmol) was added to a solution of 1-{3-cyano-5-[(ethylthio)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid (0.090 g, 0.270 mmol) in DCM (4 mL) at r.t. and the reaction was stirred for 45 minutes before 1-phenylmethanesulfonamide (0.055 g, 0.321 mmol) was added and the stirring was continued for an additional 15 hours. NaHCO3 (aq) was added and the mixture was extracted with DCM (3 times). The combined organic phase was dried and concentrated. Evaporation followed by purification by reverse phase HPLC (Kromasil C8, 21.5 x 250 mm column, flow 25 mL/min using a gradient of 0.1 M NH_4OAc and CH_3CN) gave S-ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylpyridine-3-carbothioate. Yield: 0.053 g (40 %).

1H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J=7.5), 1.65 (2H, m), 1.85 (2H, m), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J=7.5), 3.16 (2H, m), 4.55 (2H, m), 4.70 (2H, s), 7.30 (2H, m), 7.41 (3H, m), 8.31 (1H, s), 11.61 (1H, s).

MS $^m/_Z$: 487 (M+1), 485 (M-1).

Example 102

S-Ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]pyridine-3-carbothioate

Prepared in the same way as descibed in Example 101 by replacing phenylmethanesulfonamide for 1-(4-methylphenyl)methanesulfonamide. Yield: 0.065 g (48 %).

1H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J=7.5), 1.65 (2H, m), 1.85 (2H, m), 2.31 (3H,s), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J=7.5), 3.16 (2H, m), 4.55 (2H, m), 4.64 (2H, s), 7.17 (2H, m), 7.22 (2H, m), 8.31 (1H, s), 11.56 (1H, s).

MS $^m/_Z$: 501 (M+1), 499 (M-1).

Example 103

S-Ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylpyridine-3-carbothioate

Prepared in the same way as descibed in Example 101 by replacing phenylmethanesulfonamide for 1-(4-chlorophenyl)methanesulfonamide. Yield: 0.061 g (43 %).

1H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J=7.5), 1.65 (2H, m), 1.86 (2H, m), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J=7.5), 3.16 (2H, m), 4.55 (2H, m), 4.72 (2H, s), 7.31 (2H, m), 7.49 (2H, m), 8.31 (1H, s), 11.63 (1H, s).

MS $^m/_z$: 521 (M+1), 519 (M-1).

Example 104

S-Ethyl 6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylpyridine-3-carbothioate

Prepared in the same way as descibed in Example 101 by replacing phenylmethanesulfonamide for 1-(4-fluorophenyl)methanesulfonamide. Yield: 0.058 g (43 %).

1H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J=7.4), 1.64 (2H, m), 1.86 (2H, m), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J=7.5), 3.16 (2H, m), 4.55 (2H, m), 4.70 (2H, s), 7.25 (2H, m), 7.34 (2H, m), 8.31 (1H, s), 11.62 (1H, s).

MS $^m/_z$: 505 (M+1), 503 (M-1).

Example 105

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-methoxy-2-methylnicotinate

(a) Ethyl 5-methoxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

LiH (0.0223 g, 2.80 mmol) was added to a cooled (0°C) solution of ethyl 5-hydroxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (0.502 g, 2.55 mmol) in DMF (15 mL) and the resulting mixture was stirred for 1.5 h. Iodomethane (0.175 mL, 2.80 mmol) was added and the reaction was heated to 60°C for 20 h. After cooling to r.t the mixture was diluted with EtOAc (200 mL), washed with saturated NH_4Cl (3 x 100 mL), brine, dried ($MgSO_4$) and passed through silica gel. Flash chromatography (1:1 EtOAc/hexanes) furnished ethyl 5-methoxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate as a solid. Yield: 0.140g (26 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 2.68 (3H, s), 3.88 (3H, s), 4.33 (2H, q, J = 7.1 Hz), 7.31 (1H, s), 12.07 (1H, br s).

MS $^m/_z$: 212 (M+1).

(b) Ethyl 6-chloro-5-methoxy-2-methylnicotinate

A suspension of ethyl 5-methoxy-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (0.065 g, 0.31 mmol) in $POCl_3$ (15 mL) was heated to 60°C for 6 h. After cooling to r.t, the reaction mixture was concentrated under reduced pressure, diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and passed through silica gel. Concentration afforded ethyl 6-chloro-5-methoxy-2-methylnicotinate. Yield: 0.049 g (69 %). ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, J = 7.1 Hz), 2.74 (3H, s), 3.95 (3H, s), 4.40 (2H, q, J = 7.1 Hz), 7.71 (1H, s).
MS $^m/_z$: 230 (M+1).

(c)1-(5-(Ethoxycarbonyl)-3-methoxy-6-methylpyridin-2-yl)azetidine-3-carboxylic acid

A mixture of ethyl 6-chloro-5-methoxy-2-methylnicotinate (0.045 g, 0.20 mmol), azetidine-3-carboxylic acid (0.0258 g, 0.255 mmol) and DIPEA (0.205 mL, 1.18 mmol) in NMP (2.0 mL) was heated to 110°C for 4 days. After cooling to r.t, the reaction mixture was diluted with EtOAc (100 mL), washed with saturated NH_4Cl (3 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (35 % EtOAc/hexanes with 1 % HOAc) afforded 1-(5-(ethoxycarbonyl)-3-methoxy-6-methylpyridin-2-yl)azetidine-3-carboxylic acid.
MS $^m/_z$: 295 (M+1).

(d) Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-methoxy-2-methylnicotinate

A solution of 1-(5-(ethoxycarbonyl)-3-methoxy-6-methylpyridin-2-yl)azetidine-3-carboxylic acid (0.0550 g, 0.187 mmol), phenylmethanesulfonamide (0.352 g, 0.206 mmol), EDCI (0.0394 g, 0.206 mmol), HOBt x H_2O (0.0315 g, 0.206 mmol) and DIPEA (0.0977 mL, 0.561 mmol) in DCM (2.0 mL) was stirred at r.t for 18 h. The reaction mixture was diluted with EtOAc (60 mL), washed with saturated NH_4Cl (30 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (1:4 EtOAc / hexanes with 1 % AcOH) furnished ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-methoxy-2-methylnicotinate as a solid. Yield: 0.025 g (28 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.24-3.31 (1H, m), 3.77 (3H, s), 4.21-4.35 (6H, m), 4.65 (2H, s), 7.36-7.41 (5H, m), 7.44 (1H, s).
MS $^m/_z$: 448 (M+1).

Example 106

Ethyl 6-[4-({[(benzylsulfonyl)amino]carbonyl}amino)piperidin-1-yl]-5-cyano-2-methylnicotinate

(a) Ethyl 6-(4-(tert-butoxycarbonylamino)piperidin-1-yl)-5-cyano-2-methylnicotinate

Ethyl 6-chloro-5-cyanonicotinate (2.00 g, 8.90 mmol) and tert-butyl piperidin-4-ylcarbamate (1.78 g, 8.90 mmol) were dissolved in EtOH (50 mL) at room temperature. DIPEA (4.65 mL, 26.7 mmol) was added and the system heated at 94 °C for 4 h. The reaction mixture was cooled to room temperature and the solvent concentrated under reduced pressure. The material was partitioned between EtOAc (50 mL) and saturated aqueous NH_4Cl (2 x 30 mL). The organics were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. No purification was done. Yield: 3.30 g (95.4 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.46 (11H, s), 2.05-2.14 (2H, m), 2.72 (3H, s), 3.15-3.26 (2H, m), 3.71-3.83 (1H, m), 4.32 (2H, q, J = 7.1 Hz), 4.42-4.51 (1H, m), 4.58-4.67 (2H, m), 8.34 (1H, s).
MS $^m/_z$: 389 (M+1).

(b) Ethyl 6-(4-aminopiperidin-1-yl)-5-cyano-2-methylnicotinate dihydrochloride

Ethyl 6-(4-(tert-butoxycarbonylamino)piperidin-1-yl)-5-cyano-2-methylnicotinate (3.30 g. 8.50 mmol) was dissolved HCl (4 M in dioxane, 31.9 mL, 127 mmol). The reaction mixture was stirred at room temperature for 48 h and concentrated under reduced pressure to yield ethyl 6-(4-aminopiperidin-1-yl)-5-cyano-2-methylnicotinate dihydrochloride as a solid, which was used crude assuming 100 % conversion.

^{1}H NMR (400 MHz, d_6-DMSO): δ 1.31 (3H, t, J = 7.1 Hz), 1.53-1.68 (2H, m), 2.02-2.12 (2H, m), 2.65 (3H, s), 3.14-3.27 (2H, m), 3.30-3.43 (1H, m), 4.25 (2H, q, J = 7.1 Hz), 4.50-4.60 (2H, m), 8.17-8.29 (2H, m), 8.37 (1H, s).
MS $^m/_z$: 362 (M+1).

(c) Ethyl 6-[4-({[(benzylsulfonyl)amino]carbonyl}amino)piperidin-1-yl]-5-cyano-2-methylnicotinate

CDI (0.152 g, 0.934 mmol) and 1-phenylmethanesulfonamide (0.200 g, 1.17 mmol) were dissolved in DCE (2 mL) and stirred for 16 h at r.t. Ethyl 6-(4-aminopiperidin-1-yl)-5-cyano-2-methylnicotinate dihydrochloride (0.200 g, 0.554 mmol) in DCE (2 mL) and DIPEA (0.482 mL, 2.77 mmol) were added to this solution and stirred at r.t for 5 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (40 mL). The combined organics were washed with 2 N HCl (2 x 30 mL), saturated NH_4Cl (2 x 30 mL), and water (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Trituration (40 % hexanes, 40 % Et_2O, and 20% DCM) gave ethyl 6-[4-({[(benzylsulfonyl)amino]carbonyl}amino)piperidin-1-yl]-5-cyano-2-methylnicotinateas a solid. Yield: 0.185 g (68.8 %)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.1 Hz), 1.39-1.56 (2H, m), 1.88-2.00 (2H, m), 2.64 (3H, s), 3.77-3.89 (1H, m), 4.25 (2H, q, J = 7.1 Hz), 4.39-4.49 (2H, m), 4.69 (2H, s), 6.32-6.41 (1H, m), 7.29-7.45 (5H, m), 8.34 (1H, s), 9.90 (1H, s).

MS $^m/_z$: 486 (M+1).

Example 107

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperazin-1-yl)-5-cyano-2-methylnicotinate

(a) *tert*-Butyl 4-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperazine-1-carboxylate

Ethyl 6-chloro-5-cyanonicotinate (0.500 g, 2.23 mmol) and tert-butyl piperazine-1-carboxylate (0.623 g, 3.35 mmol) were dissolved in EtOH (50 mL) at r.t. DIPEA (1.16 mL, 6.68 mmol) was added and the system heated at 55 °C for 6 h. The reaction mixture was cooled to r.t and the solvent concentrated under reduced pressure. The material was partitioned between EtOAc (50 mL) and saturated aqueous NH_4Cl (2 x 30 mL). The organics were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Flash Chromatography (20 % EtOAc in Hexanes) gave *tert*-Butyl 4-(3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)piperazine-1-carboxylate.Yield: 0.743 g (89.2 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, q, J = 7.1 Hz), 1.49 (9H, s), 2.73 (3H, s), 3.53-3.61 (4H, m), 3.86-3.95 (4H, m), 4.32 (2H, q, J = 7.1 Hz), 8.36 (1H, s).
MS $^m/_z$: 375 (M+1).

(b) Ethyl 5-cyano-2-methyl-6-piperazin-1-ylnicotinate dihydrochloride

tert-Butyl 4-(3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl)piperazine-1-carboxylate (3.30 g. 8.50 mmol) was dissolved HCl (2 M in Et_2O, 2.98 mL, 5.95 mmol). The reaction mixture was stirred at r.t for 24 h and concentrated under reduced pressure to yield ethyl 5-cyano-2-methyl-6-(piperazin-1-yl)nicotinate dihydrochloride as a solid, which was used crude assuming 100 % conversion.
^{1}H NMR (400 MHz, CD_3OD): δ 1.31 (3H, t, J = 7.1 Hz), 2.67 (3H, s), 3.19-3.30 (4H, m), 3.99-4.09 (4H, m), 4.27 (2H, q, J = 7.1 Hz), 8.43 (1H, s), 9.28 (1H, m).
MS $^m/_z$: 275 (M+1).

(c) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperazin-1-yl)-5-cyano-2-methylnicotinate

CDI (0.152 g, 0.934 mmol) and 1-phenylmethanesulfonamide (0.200 g, 1.17 mmol) were dissolved in DCE (2 mL) and stirred for 16 h at r.t. Ethyl 5-cyano-2-methyl-6-(piperazin-1-yl)nicotinate dihydrochloride (0.200 g, 0.576 mmol) in DCE (2 mL) and DIPEA (0.502 mL, 2.88 mmol) were added to this solution and stirred at r.t for 5 h. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (40 mL). The combined organics were washed with 2 M HCl (2 x 30 mL), saturated NH_4Cl (2 x 30 mL), and H_2O (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product. Trituration (40 % hexanes, 40 % Et_2O, and 20% DCM then 10% MeOH in Et_2O) gave ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperazin-1-yl)-5-cyano-2-methylnicotinate as a solid. Yield: 0.156 g (57 %)
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.1 Hz), 2.66 (3H, s), 3.52-3.62 (4H, m), 3.80-3.90 (4H, m), 4.26 (2H, q, J = 7.1 Hz), 4.76 (2H, s), 7.33-7.42 (5H, m), 8.35 (1H, s), 10.5-10.6 (1H, m).
MS $^m/_z$: 472 (M+1).

Example 108

4-{[2-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid

A solution of ethyl ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate (0.050 g, 0.089 mmol) in THF (4 mL) was cooled to 0°C and treated with NaOH (1.00 M, 0.18 mL, 0.18 mmol). The reaction was warmed to r.t. and stirred for 18 h. After dilution with EtOAc (100 mL), the mixture was washed with saturated NH_4Cl (2 x 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (50 % EtOAc/hexanes with 1 % HOAc) furnished 4-{[2-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid as a solid. Yield: 0.036 g (67 %).

MS $^m/_z$: 548 (M+1).

Example 109

Ethyl 5-cyano-2-methyl-6-{3-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

a) 1-Pyridin-2-ylmethanesulfonamide

To a solution of SMOPS (4.8 g, 0.028 mol) in DMSO (dry, 50 mL) was added 2-bromomethyl pyridine HBr (5 g, 0.019 mol) at r.t.. After 40 min pH of the solution was adjusted to 8 by the addition of aqueous bicarbonate solution. The reaction mixture was extracted with EtOAc (4 x 100 mL), the organic layers were combined, dried over anhydrous sodium sulphate, filtered and the solvents were removed in vacuo. The residue was redissolved in a mixture of solvents consisting of THF (200 mL) and methanol (10 mL) and treated with a solution of sodium methoxide (4 mL, 25%) over a period of 10 min. After stirring for 40 min, the reaction mixture was concentrated in vacuo and dissolved in water (20 mL). Followed by addition of a solution of hydroxylamine-O-sulfonic acid (12.66 g, 0.099 mol), sodium acetate (7g) in water (60 mL) followed by stirring at r.t.. After 48 h pH of the solution was adjusted to 9 by the addition of aqueous bicarbonate solution and the mixture subjected to freeze drying. The solid thus obtained was treated with methanol, methanolic layer separated and concentrated. The residue was purified by flash chromatography on silica using a gradient of EtOAc in pet ether followed by EtOAc and then with MeOH in EtOAc to give 1-Pyridin-2-ylmethanesulfonamide. Yield: 400 mg (12 %).

^{1}H NMR (400 MHz, DMSO-d6) δ 4.42-4.45 (2H, m), 6.90-6.95 (2H, m), 7.33-7.39 (1H, m), 7.45-7.50(1H, m), 7.78-7.85 (1H, m), 8.53-8.59 (1H, m)
MS $^m/_z$: 173 (M+1).

b) 1-(1-oxidopyridin-2-yl)methanesulfonamide

1-Pyridin-2-ylmethanesulfonamide (100 mg, 0.55 mmol) was dissolved in DCM (2mL) and cooled in an ice bath before m-CPBA (184 mg, 0.61 mmol) dissolved in DCM (1ml) was added. Reaction was stirred at r. t. for two hours followed by removal of solvents in vacuo. The crude solid was dissolved in CH3CN/H2O(4 mL), and purified on preparative HPLC (C8, 10um, 20x250mm). 25ml/min, 5% CH3CN in 0.2% HOAc. 1-(1-Oxidopyridin-2-yl)methanesulfonamide was isolated as a light yellow solid. Yield 65mg (60 %).
MS $^m/_z$: 189 (M+1)

c) Ethyl 5-cyano-2-methyl-6-{3-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

Prepared according to method B starting from 1-(1-oxidopyridin-2-yl)methanesulfonamide.Yield=13 mg (14%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, *J* = 7.1 Hz), 2.63 (3H, s), 3.40 - 3.53 (1H, m), 4.23 (2H, q, *J* = 7.1 Hz), 4.31 - 4.51 (4H, m), 5.02 (2H, s), 7.27 - 7.49 (2H, m), 7.57 - 7.69 (1H, m), 8.20 - 8.25 (1H, m),8.29 (1H, s)
MS $^m/_z$: 460 (M+1).

Example 110

Ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-3-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to method B starting from 1-pyridin-3-ylmethanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109 step a.Yield=6 mg (7%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, *J* = 6.9 Hz), 2.63 (3H, s),3.38 - 3.49 (1H, m),4.23 (2H, q, *J* = 7.0 Hz),4.28 - 4.55 (4H, m),4.64 (2H, s),7.30 - 7.48 (1H, m),7.66 - 7.83 (1H, m),8.29 (1H, s),8.47 (1H, s),8.50 - 8.57 (1H, m)

MS $^{m}/_{z}$: 444 (M+1).

Example 111

Ethyl 5-cyano-2-methyl-6-{4-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

Prepared according to method B starting from 1-(1-oxidopyridin-2-yl)methanesulfonamide(see example 109 a and b).Yield=27 mg (28%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.72 (2H, m), 1.86 - 1.99 (2H, m), 2.47 - 2.55 (1H, m), 2.64 (3H, s), 3.12 - 3.24 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.45 - 4.60 (2H, m), 5.02 (2H, s), 7.30 - 7.49 (2H, m), 7.55 - 7.65 (1H, m), 8.25 - 8.37 (2H, m), 11.62 - 11.92 (1H, m)

MS $^{m}/_{z}$: 488 (M+1).

Example 112

Ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-3-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to method B starting from 1-pyridin-3-ylmethanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109 step a.Yield=32 mg (34%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.1 Hz), 1.55 - 1.71 (2H, m), 1.79 - 1.89 (2H, m), 2.46 - 2.56 (1H, m), 2.65 (3H, s), 3.09 - 3.21 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.49 - 4.59 (2H, m),4.73 (2H, s),7.38 - 7.50 (1H, m),7.66 - 7.78 (1H, m),8.34 (1H, s),8.47 (1H, s), 8.52 - 8.62 (1H, m), 11.58 - 11.85 (1H, m)

MS $^{m}/_{z}$: 472 (M+1).

Example 113

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

a) ethyl 5-cyano-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

Na (2.76 g, 120 mmol) was added piecewise to 22 mL ethanol and was heated at 80 °C for 45 minutes. This was added to a slurry of 2-cyanoacetamide (4.2 g, 50 mmol) in 6 mL warm

ethanol. The mixture was stirred for 20 min. followed by addition of diethyl (ethoxymethylene)malonate (10.8 g, 50 mmol). The reaction mixture was refluxed for 16h followed by cooling to room temperature. The crude product was filtered off and the solid material was triturated with 2x20 mL diethyl ether followed by 2x20 mL heptane. The solid was dried under vacuum to give ethyl 5-cyano-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate

^{1}H NMR (500 MHz, DMSO-d6): δ1.05 (3H,t, *J*=7Hz), 3.40(2H, d, *J*=7Hz), 7.88 (1H, s)

b) Ethyl 2,6-dichloro-5-cyanonicotinate

To ethyl 5-cyano-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate (1.56 g, 7.50 mmol) in toluene 15b mL was added thionyl chloride (5.35 g, 45 mmol) followed by DMF (55 mg, 75 mmol). The reaction mixture was heated at 85 °C for 16h. An additional amount of thionyl chloride (5.35 g, 45 mmol) followed by DMF (55 mg, 75 mmol) was added folowed by heating at 100 °C for 4h. The solvents were removed in vacuo for a part of the material which was used in the consecutive step.

c) Ethyl 6-chloro-5-cyano-2-(dimethylamino)nicotinate

Ethyl 2,6-dichloro-5-cyanonicotinate (147 mg, 0.600 mmol) in 1.5 mL MeCN was cooled to 0 °C followed by addition of *N*-methylmethanamine (10.5 µL, 0.150 mmol) in 0.15 mL MeCN. stirring at 0 °C for 15 min. followed by additon of an additional amount of *N*-methylmethanamine (10.5 µL, 0.150 mmol) in 0.15 mL. The reaction mixture was stirred at r.t. for 16h. The solvents were removed in vacuo and part of the material was used immediately in the next step.

d) 1-[3-cyano-6-(dimethylamino)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid

Ethyl 6-chloro-5-cyano-2-(dimethylamino)nicotinate (76 mg, 0.300 mmol) from the step above was dissolved in 1.5 mL ethanol/water 1:1 followed by addition of piperidine-4-carboxylic acid (116 mg, 0.90 mmol) was added, followed by TEA (91 mg, 0.90 mmol). The reaction mixture was heated in a single node microwave oven at 120°C for 20 min. The solvents were removed in vacuo to give 201mg crude material.

Purification was done by reverse phase HPLC. A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=50 mL/min. continuous over 3

minutes after the injection. Then changed to A/B/C 5:0:95 and flow increased to 100 mL/min. Increased to 100:0:0 over 17 minutes in steps of 5% points. Column: Kromasil C8, 250 mmx50.8 ID.Product was eluted when A/C was 70:30. This gave 1-[3-cyano-6-(dimethylamino)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid. Yield= 44 mg (42%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35(3H, t, J=7.0Hz), 1.78-1.89(2H, m), 1.99-2.01(2H, m), 2.61-2.67(1H, m), 3.3-3.5(6H, m), 3.17-3.24(2H, m), 4.28(2H, q, 7.0Hz), 4.42-4.49(2H, m), 8.13(1H, s)

e) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

1-[3-cyano-6-(dimethylamino)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid (24 mg, 0.069 mmol) was dissolved in DCM(1mL) followed by addition of TBTU (37 mg, 0.097 mmol) and DIPEA (0.047 mL, 0.28 mmol). After 2 minutes 1-phenylmethanesulfonamide (14 mg, 0.083 mmol) was added. The reaction mixture was stirred at room temperature for 6h followed by addition of .094 mL DIPEA.. Stirring at room temperature was continued for an additonal 16hr. 1-phenylmethanesulfoneamide (14 mg, 0.083 mmol) and TBTU (37 mg, 0.097 mmol) was added followed by stirring at rt for an additional 22h.

Purification was done by reverse phase HPLC: A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=20 mL/min. just after injection. Then changed to A/B/C 5:0:95. Increased to 50:0:50 over 30 min. in 9 equal steps. Then to 100:0:0 over 10 min. in 5 steps. Flow: 20 mL/min. Column: Kromasil C8, 250 mmx20 ID. This gave Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate. Yield=8 mg (23%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (3H, t, J = 7.2 Hz), 1.71-1.86 (4H, m), 2.33-2.42 (1H, m), 2.98-3.04 (2H, m), 3.05 (6H, s), 4.28 (2H, q, J = 7.2 Hz), 4.48-4.54 (2H, m), 4.65 (2H, s), 7.31-7.35 (2H, m), 7.36-7.43 (3H, m), 8.12 (1H, s).

MS $^m/_z$: 500 (M+1)

Example 114

Ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-4-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to method B starting from 1-pyridin-4-ylmethanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109 step a.Yield=20 mg (21%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.1 Hz), 1.56 - 1.70 (2H, m), 1.79 - 1.89 (2H, m), 2.46 - 2.56 (1H, m), 2.65 (3H, s), 3.08 - 3.21 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.48 - 4.58 (2H, m), 4.73 (2H, s), 7.29-7.33 (2H,m), 8.34 (1H, s), 8.58-8.62 (2H,m), 11.65 - 11.93 (1H, m)

MS $^m/_z$: 472 (M+1).

Example 115

Ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-2-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to method B starting from 1-pyridin-2-ylmethanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109 step a.Yield=7 mg (8%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30(3H, t, J = 7.1 Hz), 2.64(3H, s), 3.43 - 3.57(1H, m), 4.24(2H, q, J = 7.1 Hz), 4.36 - 4.56(4H, m), 4.80(2H, s), 7.30 - 7.57(2H, m), 7.75 - 7.89(1H, m), 8.31(1H, s), 8.49 - 8.59(1H, m), 11.52 - 11.99(1H, m)

MS $^m/_z$: 444 (M+1).

Example 116

Ethyl 5-cyano-6-[3-({[(3,5-dimethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-(3,5-dimethylphenyl)methanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109. Yield=5 mg (5%).

MS $^m/_z$: 471 (M+1).

Example 117

Isopropyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

To 1-[3-cyano-5-(isopropoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (100 mg, 0.301 mmol) were added TBTU(97mg, 0.302 mmol), dry DCM(2mL), DIPEA(0.1mL, 0.574 mmol) and the mixture was stirred at room temperature for 2.5h. The mixture was added to 1-cyclopentylmethanesulfonamide (58.8mg, 0.360 mmol), dry DCM(2ml) was added and the reaction mixture was stirred at rorrm temperature for 18h. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layers was passed through a phase separator and the solvents were removed *in vacuo*. The crude product was purified using preparative HPLC on a (Kromasil C8 10µm, 21.5x250mm) using a gradient of 25-55% acetonitrile/aqueous NH4OAc buffer pH 7 to give isopropyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate. Yield: 80 mg (56 %).

^{1}H NMR (500 MHz, DMSO-d6) δ 1.22-1.93 (12H, m), 1.30 (6H,app d, *J=6.2Hz),* 2.11-2.20 (1H, m), 2.64 (3H, s), 2.64-2.69 (1H, m), 3.14-3.21 (2H, m), 3.42 (2H, d, *J=7.0Hz)*, 4.51-4.57 (2H, m), 5.08 (1H, app q, *J=6.2Hz*), 8.32 (1H, s), 11.71 (1H, s).
MS $^m/_z$: 477.3 (M+1), 475.3 (M-1).

Example 118

Ethyl 5-cyano-6-[4-({[(2,5-dimethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-(2,5-dimethylphenyl)methanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109. Yield=18 mg (18%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, *J* = 7.1 Hz), 1.59 - 1.76 (2H, m), 1.83 - 1.95 (2H, m), 2.25 (3H, s), 2.33 (3H, s), 2.47 - 2.56 (1H, m), 2.65 (3H, s), 3.11 - 3.23 (2H, m), 4.25 (2H, q, *J* = 7.1 Hz), 4.51 - 4.60 (2H, m), 4.64 (2H, s), 6.95 (1H, s), 7.04 - 7.15 (2H, m), 8.34 (1H, s), 11.54 - 11.87 (1H, m)
MS $^m/_z$: 499 (M+1).

Example 119

Ethyl 5-cyano-6-[4-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

a) Sodium (4-isopropylphenyl)methanesulfonate

1-(chloromethyl)-4-isopropylbenzene (2.53 g, 15.0 mmol) and disodium sulfite (2.46, 19.5 mmol) were added to a mixture of water (8mL) and acetone (0.8mL). The reaction mixture was heated in a microwave oven, single node heating, at 150 degr. for 5 min. The reaction mixture was transfered to a round-bottome flask with acetone (40mL) and water.(4mL) The mixture was refluxed for 5.5h. The solvents were removed in vacuo and the remaining solids were slurried in 20 mL hot abs. ethanol and the crystals were filtered off. The filter cake was rinsed with 10 mL abs. ethanol followed by 2x15 mL heptane and finally dried under vacuum for 2h. This gave Sodium (4-isopropylphenyl)methanesulfonate. Yield=3.3 g.(92%)

b) 1-(4-isopropylphenyl)methanesulfonamide

Sodium (4-isopropylphenyl)methanesulfonate (1.9 g, 8.0 mmol) folowed by dioxane (32mL) and thionyl chloride(2.92 mL, 40 mmol) was distributed into 4 vials and heated at 100°C for 20 minutes each using fixed hold time. The reaction mixtures were combined and the solvents were removed in vacuo. A solution of ammonia in THF (40 mL) was added at r.t. and the reaction mixture was stirred for for 16h. Water (30mL) was added and the organic phase was separated. The aq. phase was extracted with 2x30 mL ethyl acetate. The combined organic phases were dried over sodium sulphate, filtered and the solvents were removed in vacuo. The crude was purified by flash chromatography on Si-gel with heptane/ethyl acetate 2:1 (Rf of product=0.22) as eluent to give 1-(4-isopropylphenyl)methanesulfonamide. Yield=376 mg, 1.76 mmol. (22%)

c) Ethyl 5-cyano-6-[4-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (159 mg, 0.500 mmol) was dissolved in DCM (4mL)and HATU(265 mg, 0.700 mmol)) was added, followed by DIPEA (0.341mL, 2mmol). The reaction mixture was stirred at room temperature for 5 minutes before the addition of 1-(4-isopropylphenyl)methanesulfonamide (128 mg, 0.600mmol). Stirring at rt was continued over 18h. The reaction mixture was concentrated and then dissolved in DMSO (8mL).

Purification was done by reverse phase HPLC. A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=50 mL/min. continuous over 3

minutes after the injection. Then changed to A/B/C 5:0:95 and flow increased to 100 mL/min. Increased to 100:0:0 over 17 minutes in equal steps, each of 5% points. The product was eluted when swithing to pure acetonitrile. Column: Kromasil C8, 250 mmx50.8 ID. This gave Ethyl 5-cyano-6-[4-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate. Yield 0.144 g (56%)

^{1}H-NMR (400 MHz, DMSO-d6) δ 1.18(6H, d, J = 6.8 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.54-1.67 (2H, m), 1.75-1.85 (2H, m), 2.20-2.30 (1H, m), 2.65 (3H, s), 2.80-2.89 (1H, m), 3.18-3.28 (2H, m), 4.19 (2H, s), 4.26 (2H, q, J = 7.1 Hz), 4.38-4.47 (2H, m), 7.09-7.18 (4H, m), 8.32 (1H, s).

MS $^m/_z$: 513 (M+1)

Example 120

Benzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

a) Benzyl 6-chloro-5-cyano-2-methylnicotinate

6-Chloro-5-cyano-2-methylnicotinoyl chloride (120 mg, 0.56 mmol) was dissolved in dry THF(4ml), DIPEA(0.2ml) and phenylmethanol(0.059ml) were added. The reaction mixture was stirred at r.t. for 15h. The solvents were removed in vacuo to give benzyl 6-chloro-5-cyano-2-methylnicotinate which was used in the next step without purification.

b) Benzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

Benzyl 6-chloro-5-cyano-2-methylnicotinate (129 mg, 0.45 mmol) was dissolved in THF(2ml), MeOH(2ml), DIPEA(0.1mL,0.574 mmol) and *N*-(benzylsulfonyl)piperidine-4-carboxamide (140 mg, 0.496 mmol) were added. The reaction mixture was heated to 120C for 5min using microwave single node heating. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layer was passed through a phase separator and the solvents were removed *in vacuo*. The crude product was purified using preparative HPLC on a (Kromasil C8 10µm, 21.5x250mm) using a gradient of 30-55% acetonitrile/aqueous NH4OAc buffer pH 7 to give

Benzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate. Yield=38 mg (15%).

^{1}H NMR (500MHz, DMSO-d6)δ 1.64(2H, m), 1.84 (2H), 2.58 (1H, m), 2.66 (3H, s), 3.15 (2H, m), 4.54 (2H, m), 4.69 (2H, s), 5.30 (2H, s), 7.28-7.49 (10H, m), 8.38 (1H, s), 11.61 (1H, s).

MS $^m/_z$: 533.3 (M+1), 531.3 (M-1).

Example 121

Ethyl 5-cyano-2-methyl-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

a) 1-(4-methylphenyl)methanesulfonamide

To a stirred solution of SMOPS (5.646 g, 0.0324 mol) in DMSO (dry, 50 mL) was added alpha-bromo-p-xylene (5 g, 0.027 mol) at r.t. and continued stirring for 45 min. The reaction mixture was extracted with EtOAc (4 x 100 mL), the organic layers were combined, dried over anhydrous sodium sulphate and the solvents were removed in vacuo. The residue was redissolved in THF (100 mL) and methanol (25 mL) followed by addition of sodium methoxide (5.8 mL, 0.027 mol, 25%). After stirring for 15 min, the reaction mixture was concentrated and dissolved in water (10 mL). A solution of hydroxylamine-O-sulfonic acid (17.31g, 0.1350 mol) and sodium acetate (7g) in H_2O (40 mL) was added to the reaction mixture which was stirred at r.t. for 12 h. The pH of the solution was adjusted to 9 by addition of aqueous bicarbonate solution and the mixture was extracted with EtOAc (3x50 ml), washed with brine, dried over (Na_2SO_4), and the solvents were removed in vacuo. The residue thus obtained was treated with water (100 mL) and stirred for 10 min. Solid obtained was filtered and dried to afford 1-(4-methylphenyl)methanesulfonamide. Yield= 3.3 g, (66 %).

^{1}H NMR (300 MHz, DMSO-d6) δ 2.55(3H, s), 4.05(2H, s), 6.8 (2H,s), 7.1-7,3 (4H, m)

b) 1-(4-methylcyclohexyl)methanesulfonamide

PtO_2 (2 g) was added to stirred solution of 1-(4-methylphenyl)methanesulfonamide (2 g, 0.0180 mol) in acetic acid (50 mL) at r.t. in a parr shaker and continued stirring for ~ 48 h under H_2 (pressure at 6 kg/cm^2). After completion of the reaction, reaction mixture was filtered, washed with acetic acid (30 mL) and concentrated. The crude product was purified using flash column chromatography using 10 % EtOAc in pet. ether to afford 1-(4-methylcyclohexyl)methanesulfonamide. Yield=520 mg (25.2%).

^{1}H NMR (300 MHz, DMSO-d6) δ 0.83-2.2(13H, m) 2.84-2.94 (2H m), 6.74 (2H, s)

MS $^{m}/_{z}$: 191.8 (M+1).

c) Ethyl 5-cyano-2-methyl-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

Prepared according to method B starting from 1-(4-methylcyclohexyl)methanesulfonamide.Yield=23 mg (23%).

^{1}H NMR (400 MHz, DMSO-d6) ? 0.80 - 0.97 (4H, m), 0.99 - 1.21 (2H, m), 1.30 (3H, t, J = 7.2 Hz), 1.39 - 1.57 (4H, m), 1.57 - 1.73 (2H, m), 1.78 - 1.98 (3H, m), 2.00 - 2.11 (1H, m), 2.47-2.6 (1H, m), 2.64 (3H, s), 3.12 - 3.23 (2H, m), 3.22 - 3.40 (3H, m), 4.25 (2H, q, J = 7.1 Hz), 4.47 - 4.61 (2H, m), 8.33 (1H, s), 11.66 - 11.81 (1H, m)

MS $^{m}/_{z}$: 491 (M+1).

Example 122

Ethyl 5-cyano-6-[3-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (145 mg, 0.500 mmol)was dissolved in 4 mL DCM/DMF 1:1. HBTU (0.265,.0.700 mmol) and DIPEA (0.341mL, 2 mmol) were added. Further, 2 mL DMF was added. 1-(4-isopropylphenyl)methanesulfonamide (128 mg, 0.600 mmol) was added.and the reaction mixture was stirred for 18h. Extra HBTU (0.095 g, 0.25 mmol) and DIPEA (0.17 mL, 1 mmol.) was added and stirring at rt was continued for 22h. The solution was concentrate and then dissolved in 8 mL DMSO. The product was isolated using by reverse phase HPLC. A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=50 mL/min. continuous over 3 minutes after the injection. Then changed to A/B/C 5:0:95 and flow increased to 100 mL/min. Increased to 100:0:0 over 17 minutes in equal steps, each of 5% points. Column: Kromasil C8, 250 mmx50.8 ID.

This gave Ethyl 5-cyano-6-[3-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate. Yield 0.198 g, (82 %)

^{1}H-NMR (400 MHz, *DMSO-d6*): δ 1.18 (6H, d, J = 6.9 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.63 (3H, s), 2.73-2.87 (1H, m), 3.17-3.26 (1H, m), 4.21-4.27 (4H, m), 4.27-4.48 (4H, m), 7.08 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz), 8.28 (1H, s).

MS $^{m}/_{z}$: 485 (M+1)

Example 123

Ethyl 5-cyano-2-methyl-6-[4-({[(2-phenylethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to method B starting from 2-phenylethanesulfonamide.Yield=22 mg (22%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.1 Hz), 1.50 - 1.65 (2H, m), 1.82 - 1.94 (2H, m), 2.50 - 2.53 (1H, m), 2.64 (3H, s), 2.93 - 3.00 (2H, m), 3.10 - 3.21 (2H, m), 3.58 - 3.70 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.46 - 4.58 (2H, m), 7.16 - 7.37 (5H, m), 8.33 (1H, s), 11.69 - 11.85 (1H, m)

MS $^m/_z$: 485 (M+1).

Example 124

Ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-2-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to method B starting from 1-pyridin-2-ylmethanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109 step a.Yield=7 mg (7%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.31 (3H, t, J = 7.1 Hz), 1.61 - 1.74 (2H, m), 1.83 - 1.92 (2H, m), 2.47 - 2.56 (1H, m), 2.65 (3H, s), 3.13 - 3.25 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.48 - 4.58 (2H, m), 4.77 (2H, s), 7.35 - 7.42 (1H, m), 7.46 (1H, d, J = 7.9 Hz), 7.79 - 7.88 (1H, m), 8.34 (1H, s), 8.52 - 8.58 (1H, m), 11.41 - 11.70 (1H, m)

MS $^m/_z$: 472 (M+1).

Example 125

Ethyl 5-cyano-6-[3-({[(2,5-dimethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-(2,5-dimethylphenyl)methanesulfonamide 1-(2,5-dimethylphenyl)methanesulfonamide which was prepared from the corresponding bromide in a similar fashion to example 109.Yield=6 mg (6%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.2 Hz),2.24 (3H, s),2.34 (3H, s),2.63 (3H, s),3.52 - 3.68 (1H, m),4.24 (2H, q, J = 7.1 Hz),4.31 - 4.41 (2H, m),4.41 - 4.51 (2H, m),4.70 (2H, s),7.01 (1H, s),7.05 - 7.15 (2H, m),8.31 (1H, s),11.76 - 12.09 (1H, m)
MS $^m/_z$: 471 (M+1).

Example 126

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloro-2-methylnicotinate

a) Ethyl 5-chloro-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

Ethyl 2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (2.00 g, 11.0 mmol), (Raileanu D., et. al. Tetrahedron , Vol 30 pp 623-32, 1974) was dissolved in DMF (35 mL) under a nitrogen atmosphere. NCS (1.53g, 11.5 mmol) taken upp in DMF (5.0 mL) at r.t. The reaction mixture was heated at 100°C for 1h. An additional amount of NCS (500mg, 3.8 mmol) was added and the reaction mixture was stirred for 0.5h. The reaction mixture was diluted with DCM were washed with water and brine once each. The aqueous phase was extracted with DCM twice and the combined organic phases were passed through a phase separator and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica (Biotage horizon)first EtOAc/heptane 1:1 followed by EtOAc to give ethyl 5-chloro-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate as a yellow solid Yield=1.362g(52%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.37 (3H, t, J = 7.3 Hz), 2.74 (3H, s), 4.32 (2H, q, J = 7.3) Hz, 8.19 (1H, s)

b) ethyl 5,6-dichloro-2-methylnicotinate

Ethyl 5-chloro-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.2g, 5.1 mmol)was dissolved in DCM (25mL) followed by addition of oxalylchloride (2.2mL, 26 mmol). Two drops of DMF was added and the mixture was heated at 42°C. After 3 h oxalylchloride (2 mL, 24 mmol) was added. After an hour further oxalylchloride (1.1ml, 13 mmol) and DMF (0.03mL) were added and the reaction mixture was stirred at 50°C over night. The reaction mixture was diluted with DCM and poured onto an ice/water mix. The phases were separated and the organic phase was washed with sat.NaHCO3x2 followed by brine. The combined aqueous phases were extracted with DCM and the combined organic phases were filtered through a phase separator and the solvents were removed in vacuo. The crude product was co

–concentrated with DCM three times which gave ethyl 5,6-dichloro-2-methylnicotinate as a dark brown solid. Yield , 0.949g .(52%)

^{1}H NMR (400 MHz, DMSO-d6) δ 1.32 (3H, t, J = 8.0 Hz), 2.67 (3H, s), 4.32 (2H, q, J = 7.2 Hz), 8.37 (1H, s)

c)Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloro-2-methylnicotinate

Ehyl 5,6-dichloro-2-methylnicotinate (202mg 0.846 mmol) and *N*-(benzylsulfonyl)azetidine-3-carboxamide (237mg, 0.930 mmol) were dissolved in EtOH (5mL), water (8mL) and MeCN (3mL). Heated in microwave oven, single node heating, for 20 minutes at 120°C. TEA (0.47 mL, 3.4 mmol) was added and the mixture was heated in microwave oven for 20 minutes at 120°C. The reaction mixture was diluted with DCM and the organics were washed with 2%KHSO4 twice. The combined aqueous phases were extracted with DCM. The combined organic phases were passed through a phaseseparator followed by removal of the solvents *in vacuo*. The crude product was purified using preparative HPLC on a (Kromasil C8. 50.8 x 300 mm), in order to avoid precipitation the the compound was loaded ont o the column using 5% acetonitrile/aqueous NH4OAc buffer pH 7. The product was eluted us ing a gradient of 5-90% acetonitrile/aqueous NH4OAc buffer pH 3 to give pure Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloro-2-methylnicotinate. Yield: 204 mg (53 %).

^{1}H NMR (400 MHz, DMSO-d6) δ1.28 (3H, t, J = 7.3 Hz) , 2.58 (3H, s), 3.53 - 3.43 (1H, m), 4.15-4.42 (6H, m), 4.74 (2H, s), 7.25-7.43 (5H, m), 7.93 (1H, s), 11.77 (1H, s),

$MS^m/_z$: 452 (M+1)

Example 127

Ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

a) Azetidin-3-ylacetic acid

[1-(*tert*-Butoxycarbonyl)azetidin-3-yl]acetic acid (1.0g, 4.65 mmol) was dissolved in DCM (8mL) followed by addition of TFA (5mL). The reaction mixture was stirred at r.t. for 2h. The solvents were removed and the crude Azetidin-3-ylacetic acid (1.31g, TFA left) was used in step b without purification.

^{1}H-NMR (500MHz, DMSO-d6) δ2.61-2.65(2H, m), 2.98-3.09 (1H, m), 3.68-3.77(2H, m), 3.95-4.03(2H, m)

b) {1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidin-3-yl}acetic acid

Azetidin-3-ylacetic acid (460.5 mg , 5.00 mmol) from previous step was dissolved in EtOH(8mL) and ethyl 6-chloro-5-cyano-2-methylnicotinate (1.02 g,), DIPEA(2mL) were added. The reaction mixture was heated at 100°C for 5min using microwave single node heating. NH_4Cl(aq) was added and the mixture was extracted with DCM three times. The combined organic layers were run through a phase separator and the solvents were removed in vacuo. The crude product was purified by prepHPLC.

Column: Kromasil C8 10µm, 50.8x300mm, Mobilephase A: 100% AcN, Mobilephase B 5%, AcN, 95% NH_4AcO(aq) (pH7), Gradient: 20=>60% A over 60min, Flow: 50ml/min and UV: 280nm.

This gave {1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidin-3-yl}acetic acid yield=526mg.(43.3%)

^{1}H-NMR (500MHz, DMSO-d6) δ?1.29 (3H, t, *j=7.1*), 2.60 (3H, s), 2.63-2.66 (2H, m). 2.93-3.02 (1H, m), 3.95-4.05(2H, m), 4.34 (2H, q , *j=7.1*), 4.37-4.47(2H, m)

c) Ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

{1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidin-3-yl}acetic acid (130mg, 0.429 mmol), TBTU(190mg, 0.592 mmol), DIPEA(0.2mL, 1.15 mmol) were dissolved in dry DCM(4ml) and the mixture was stirred at room temperature for 1h 20min. The mixture was added to 1-phenylmethanesulfonamide (100 mg, 0.584 mmol)and the reaction mixture was stirred at room temperature for 25h. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layer was passed through a phase separator and the solvents were removed in vacuo. The crude product was purified using preparative HPLC on a (Kromasil C8 10µm, 21.5x250mm) using a gradient of 25-45% acetonitrile/aqueous NH4OAc buffer pH 7 to give ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-methylnicotinate. Yield=119 mg (61 %)

^{1}H-NMR (500MHz, DMSO-d6) δ?.30 (3H, t, *J=7.2Hz*), 2.62 (3H, s), 2.69 (2H, m), 3.05 (1H, m), 4.02 (2H, m), 4.23 (2H, q, *J=7.2Hz*), 4.47 (2H, m), 4.70 (2H,s), 7.31 (2H, m), 7.41 (3H, m), 8.28 (1H, s), 11.67 (1H, s).

$MS^m/_z$: 457.1 (M+1), 455.0(M-1).

Example 128

Ethyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-cyclopentylmethanesulfonamide.Yield=10 mg (10%).

MS $^{m}/_{z}$: 471 (M+1).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.18 - 1.28 (2H, m), 1.30 (3H, t, *J* = 7.1 Hz), 1.43 - 1.53 (2H, m), 1.54 - 1.69 (4H, m), 1.80 - 1.95 (4H, m), 2.08 - 2.22 (1H, m), 2.22 (3H, s), 2.65 - 2.69 (1H, m), 3.11 - 3.23 (2H, m), 3.38 (2H, d, *J* = 6.8 Hz), 4.25 (2H, q, *J* = 7.1 Hz), 4.48 - 4.59 (2H, m), 8.33 (1H, s), 11.48 - 12.17 (1H, m)

MS $^{m}/_{z}$: 463 (M+1).

Example 129

Ethyl 5-cyano-6-[3-(2-{[(4-fluorobenzyl)sulfonyl]amino}-2-oxoethyl)azetidin-1-yl]-2-methylnicotinate

{1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidin-3-yl}acetic acid (130 mg, 0.43 mmol), TBTU(190mg, 0.59 mmol), DIPEA(0.2mL, 1.2 mmol) were dissolved in dry DCM(4mL) and the reaction mixture was stirred at room temperature for 1h 20min. The mixture was added to 1-(4-fluorophenyl)methanesulfonamide (189 mg, 0.53 mmol) and the reaction mixture was stirred at room temperature for 25h. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layers was passed through a phase separator and the solvents were removed *in vacuo*. The crude product was purified using preparative HPLC on a (Kromasil C8 10µm, 21.5x250mm) using a gradient of 25-45% acetonitrile/aqueous NH4OAc buffer pH 7 to give ethyl 5-cyano-6-[3-(2-{[(4-fluorobenzyl)sulfonyl]amino}-2-oxoethyl)azetidin-1-yl]-2-methylnicotinate. Yield = 134 mg (66%).

^{1}H-NMR (500MHz, DMSO-d6): δ 1.30 (3H, t, *J=7.2Hz*), 2.62 (3H, s), 2.70 (2H, m), 3.04 (1H, m), 4.02 (2H, m), 4.23 (2H, q, *J=7.2Hz*), 4.46 (2H, m), 4.71 (2H, s), 7.26 (2H, m), 7.35 (2H, m), 8.28 (1H, s), 11.69 (1H, s).

MS($^{m}/_{z}$): 475.1 (M+1), 473.0 (M-1).

Example 130

Ethyl 5-cyano-6-[4-({[(3-fluoro-4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-(3-fluoro-4-methylphenyl)methanesulfonamide, which was prepared from the corresponding bromide in a similar fashion to example 109 step a.Yield=2 mg (2%).

MS $^{m}/_{z}$: 503 (M+1).

Example 131

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-methylnicotinate

a) 1-[3-chloro-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid

Ethyl 5,6-dichloro-2-methylnicotinate (428mg, 1.79 mmol) was dissolved in MeCN (6mL) followed by addition of piperidine-4-carboxylic acid (255mg, 1.74 mmol), Water (9mL) and TEA (1.5 mL, 10.8 mmol) were added. The reaction mixture was heated for 15min at 120°C in a single node microwave oven. An additional amount of piperidine-4-carboxylic acid (128mg, 0.34 mmol) and TEA (0.5mL, 3.60 mmol) were added and the mixture was heated in a single node microwave oven for 15min at 120°C. The reaction mixture was diluted with DCM and washed with 2%KHSO4. The aqueous phase was extracted twice with DCM and the combined organic phases were filtered through a phase separator and followed by removal of solvents *in vacuo*. The crude was co-concentrated with DCM to give 1-[3-chloro-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid. Yield=391 mg (60%).

^{1}H-NMR (400 MHz, DMSO-d6) δ 1.29 (3H, t, J = 7.1 Hz), 1.71 - 1.58 (2H, m), 1.96 - 1.85 (2H, m), 2.59 (3H, s), 3.03 - 2.91 (2H, m), 4.02 - 3.91 (2H, m), 4.24 (2H, q, J = 7.1 Hz,), 8.02 (1H, s), 12.43 - 12.07 (1H, bs).

b)Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-methylnicotinate

1-[3-chloro-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (391 mg, 1.08 mmol), DIPEA (0.9 mL, 5.4 mmol)) and TBTU (404mg, 1.25 mmol) were dissolved in dry DCM (8 mL) and stirred for 15min at room temperature followed by addition of 1-Phenylmethanesulfonamide (221 mg, 1.30 mmol). The reaction mixture was stirred over night after which an additional amount of TBTU (14mg, 0.044 mmol) and 1-

Phenymethanesulfoneamide (8 mg, 0.047 mmol) were added. The reaction mixture was then stirred for another 3h before it was diluted with DCM and washed twice with 1% KHSO4(aq)x2. The aqueous phase was extracted with twice with DCM and the combined organic phases were passed through a phase separator and followed by removal of solvents in vacuo. The crude product was purified using preparative HPLC on a (Kromasil C8, 55 x 300mm), in order to avoid precipitation the the compound was loaded ont o the column using 5% acetonitrile/aqueous NH4OAc buffer pH 7. The product was eluted using a gradient of 30-100% acetonitrile/aqueous NH4OAc buffer pH 3. The fractions containing the product was concentrated *in vacuo*, dissolved in ethyl acetate and washed with brine. The aqueous phase was extracted twice with ethyla cetate and the combinde organic phases were concentrated in vacuo to give Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-methylnicotinate as a white/yellow solid. Yield=267 mg(51%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.29 (3H, t, J = 7.1 Hz), 1.74 - 1.59 (2H, m), 1.84 - 1.74 (2H, m), 2.49 (1H,s), 2.60 (3H, s), 2.86 (2H, t, J = 12.7 Hz), 4.10 - 4.00 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.67 (2H, s), 7.44 - 7.23 (5H, m), 8.03 (1H, s), 11.57 (1H, s)
MS $^m/_z$: 480(M+1).

Example 132

4-fluorobenzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

a) 4-fluorobenzyl 6-chloro-5-cyano-2-methylnicotinate
Ethyl 5,6-dichloro-2-methylnicotinate (120, 0.56 mmol) was dissolved in dry THF(4mL), DIPEA (0.2mL, 1.15 mmol) and (4-fluorophenyl)methanol (0.062 mL, 0.57 mmol) were added. The reaction mixture was stirred at r.t. for 15h. The solvents were removed in vacuo and the crude product was used in the next step without purification.

b) 4-fluorobenzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

The crude 4-fluorobenzyl 6-chloro-5-cyano-2-methylnicotinate (137 mg, 0.47 mmol) was dissolved in THF(2mL), MeOH(2mL), DIPEA(0.1mL) and *N*-(benzylsulfonyl)piperidine-4-carboxamide (140 mg, 0.49mmol) were added. The reaction mixture was heated to 120°C for 5min using a microwave single node heating. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layer was passed through a phase

separator and the solvents were remived *in vacuo*. The crude product was purified using preparative HPLC on a (Kromasil C8 10µm, 21.5x250mm) using a gradient of 30-55% acetonitrile/aqueous NH4OAc buffer pH 7 to give 4-fluorobenzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate. Yield=39 mg (16%).

^{1}H NMR (500MHz, DMSO-d6)δ 1.64 (2H, m), 1.84 (2H, m), 2.58 (1H, m), 2.65 (3H, s), 3.15 (2H, m), 4.54 (2H, m), 4.69 (2H, s), 5.27 (2H, s), 7.23 (2H, m), 7.29 (2H, m), 7.40 (3H, m), 7.54 (2H, m), 8.38 (1H, s), 11.61 (1H, s).

LCMS$^+/_z$: 551.2 (M+1), 549.3 (M-1).

Example 133

Ethyl 5-cyano-6-[4-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (95 mg, 0.30 mmol) was dissolved in DCM (1mL) and HATU (148 mg, 0.39 mmol) followed by DIPEA (155 mg, 1.20mmol) were added. The mixture was stirred at rt for 5 min. before the addition 1-(4-ethylphenyl)methanesulfonamide (66 mg, 0.33 mmol), made from the corresponding sulfonyl chloride in a similar manner to example 65b. The reaction mixture was stirred for 18h followed buy addition of 1-(4-1-(4-ethylphenyl)methanesulfonamide (10 mg, 0.05 mmol) in 0.2 mL DCM, followed by HATU (20 mg, 0.053 mmol) and stirring at rt was continued for 22h. The solvents were removed in vacuo and the crude material pas dissolved in DMSO (10 mL) and purified by reverse phase preparative HPLC. Solvents used: A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=20 mL/min. Increased to flow=100 mL/min. 3 min. after the injection. Then changed to A/B/C 5:0:95. Increased to 100:0:0 over 20 min. in 9 equal steps. Column: Kromasil C8, 250 mmx50.8 ID. The relevant fractions was concentrated and freeze-dried over night to give .0.071 g of the title compound. The Na-salt was made by slurrying the material in acetonitrile (0.4 mL) and adding 1.0 eq. 0.1 M NaOH (1.42 mL) and some water (ca. 10 mL). After stirring for 5 min. almost all material had gone into solution. The solids were removed by filtration and the solution phase was freeze-dried. This gave ethyl 5-cyano-6-[4-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate. Yield=0.076 g. (49%)

1H NMR (400 MHz, DMSO-d6)δ 1.17 (3H, t, J = 7.6 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.54-1.67 (2H, m), 1.76-1.85 (2H, m), 2.20-2.30 (1H, m), 2.56 (2H, q, J = 7.6 Hz), 2.65 (3H, s), 3.17-3.27 (2H, m), 4.20 (2H, s), 4.26 (2H, q, J = 7.1 Hz), 4.39-4.47 (2H, m), 7.09 (2H, br d, J = 8.1 Hz), 7.15 (2H, br d, J = 8.1 Hz), 8.32 (1H, s).

MS $^{m}/_{z}$: 499 (M+1)

Example 134

Prepared according to method B starting from 1-(3,4-difluorophenyl)methanesulfonamide, made from the corresponding sulfonyl chloride in a similar manner to example 65b. Yield=4 mg (4%).

MS $^{m}/_{z}$: 479 (M+1).

Example 135

Ethyl 5-cyano-6-[4-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (40 mg 0.126 mmol)was dissolved in 0.5 mL DCM and TBTU (57 mg, 0.18 mmol) and DIPEA (0.064mL, 0.38 mmol) were added. The solution was stirred at rt for 5 min followed by addition to 1-(4-methoxyphenyl)methanesulfonamide (32 mg, 0.16 mmol), which was prepared from the corresponding chloride in a similar fashion to example 109, in DCM. The reaction mixture was stirred for 2.5 days followed by purification by reverse phase HPLC. Solvents used: A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=20 mL/min. just after in jection. Then changed to A/B/C 5:0:95. Increased to 50:0:50 over 30 min. in 9 equal steps. Then to 100:0:0 over 10 min. in 5 steps. Flow: 20 mL/min. Column: Kromasil C8, 250 mmx20 ID. The material stuck on the column and did not elute until A/B/C was 95/0/5 to 100/0/0.

For the relevant fractions the organic solvents were removed *in vacuo* followed by freeze drying. 1 eq. 0.1 M NaOH was added. The material was freeze dried again to give ethyl 5-cyano-6-[4-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate. Yield=34 mg (45%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.32 (3H, d, *J* = 7.1 Hz, 1.55-1.68 (2H, m), 1.77-1.86 (2H, m), 2.27-2.36 (1H, m), 2.66 (3H, s), 3.16-3.25 (2H, m), 3.74 (3H, s), 4.22-4.30 (4H, m), 4.42-4.51 (2H, m), 6.85 (2H, br d, *J* = 8.5 Hz), 7.16 (2H, br d, *J* = 8.5 Hz), 8.33 (1H, s).
MS $^m/_z$: 523 (M+1)

Example 136

Ethyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (143mg, 0.45 mmol) was dissolved in dry DCM (4mL), TBTU(168 mg, 0.52 mmol)) and DIPEA(0.16ml, 0.92 mmol) were added. The mixture was stirred at room temperature for 30min and 1-(3-methylphenyl)methanesulfonamide (103 mg, 0.56 mmol) was added. The reaction mixture was stirred at room temperature for 22h. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layer was passed through a phase separator and the solvents were removed *in vacuo*.. The crude product was purified using preparative HPLC on a (Kromasil C8 10µm, 21.5x250mm) using a gradient of 25-45% acetonitrile/aqueous NH_4OAc buffer pH 7 to give ethyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate. Yield=160 mg (73%).

^{1}H NMR (500MHz, DMSO-d6): δ1.31 (3H, t, *J=7.0*), 1.64 (2H, m), 1.82 (2H, m), 2.31 (3H, s), 2.59 (1H, m), 2.65 (3H, s), 3.14 (2H, m), 4.26 (2H, q, *J=7.0*), 4.54 (2H, m), 4.65 (2H, s), 7.10 (2H, m), 7.21 (1H, m), 7.29 (1H, m), 8.35 (1H, s), 11.58 (1H, s).
MS$^m/_z$: 485.2 (M^{+1}), 483.2 (M^{-1}).

Example 137

Ethyl 5-cyano-6-[3-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (145 mg, 0.500 mmol) was dissolved in 2 mL DCM/DMF 1:1 and TBTU (265 mg, 0.700 mmol), DIPEA (0.34 mL, 2 mmol) and 1 mL DMF. The mixture was stirred at rt for 5 min before the addition of 1-(4-ethylphenyl)methanesulfonamide (120 mg, 0.600mmol), made from the corresponding sulfonyl chloride in a similar manner to example 65b, in 1 mL DCM. The

reaction mixture was stirred over week-end folllowed by addition of more -(4-ethylphenyl)methanesulfonamide (10 mg, 0.05 mmol) in 0.2 mL DCM, followed by extra TBTU (20 mg, 0.05 mmol) and stirring at rt was continued for 22h further. The solvents were removed in vacuo followed by addition of DMSO (10 mL).

Purification was performed by reverse phase HPLC. Solvents used: A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=20 mL/min. Increased to flow=100 mL/min. 3 min. after the injection. Then changed to A/B/C 5:0:95. The flow had to be reduced to 50 mL/min. (flow=100 mL/min. gave automatic cut-off due to increase in internal pressure). Increased to 50:0:50 over 15 min. in 5 steps. The to 100:0:0 over 15 min. in 5 steps. Column: Kromasil C8, 250 mmx50.8 ID. The relevant fraction was concentrated in vacuo and freeze-dried over night. This gave 0.111 g product. The Na-salt was made by slurrying the material in acetonitrile (1 mL) and adding 1.0 eq. 0.1 M NaOH (2.36 mL) and some water (ca. 10 mL). After stirring for 5 min. almost all material had gone into solution. The solids were removed by filtration (syringe+filter) and the liquid was freeze-dried. This gave Ethyl 5-cyano-6-[3-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate. Yield=120 mg (49%).

1H NMR (400 MHz, DMSO-d6) δ 1.16 (3H, t, J = 7.6 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.55 (2H, q, J = 7.6 Hz), 2.64 (3H, s), 3.15-3.25 (1H, m), 4.22-4.27 (4H, m), 4.27-4.40 (4H, m), 7.05 (2H, br d, J = 8.0 Hz), 7.15 (2H, br d, J = 8.0 Hz), 8.28 (1H, s).

MS $^{m}/_{z}$: 471 (M+1)

Example 138

Ethyl 5-chloro-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

A solution of 1-[3-Chloro-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (235 mg, 0.788 mmol), DIPEA (686µl, 3.94 mmol) and TBTU (303mg, 0.945 mmol) in dry DCM (5mL) was stirred for 10min at rt followed by addition of a solution of 1-(4-methylphenyl)methanesulfonamide (175 mg, 0.945 mmol) in dry DCM (1mL). The reaction mixture was stirred over night followed by addition 2% KHSO4(aq), the phases were separated and the organic phase was washed with 2% KHSO4(aq). The aqueous phase was extracted twice with DCM and the combined organic phases were filtered through a phase separator and the solvents were removed *in vacuo*. The crude product was purified using

preparative HPLC on a (Kromasil C8, 50.8 x 300mm), in order to avoid precipitation the the compound was loaded ont o the column using 5% acetonitrile/aqueous NH4OAc buffer pH 7. The product was eluted using a gradient of 5-90% acetonitrile/aqueous NH4OAc buffer pH 3 to give Ethyl 5-chloro-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate as a white solid after freeze drying. Yield=289 mg (78 %).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.28 (3H, t, J = 7.4 Hz), 2.28 (3H, s), 2.59 (3H, s,), 3.41-3.53(1H, m), 4.16-4.29 (4H, m), 4.29-4.39(2H, m), 4.67 (2H, s), 7.11-7.25(4H, m), 7.93 (1H, s), 11.71 (1H, s).
MS $^m/_z$: 466(M+1).

Example 139

Ethyl 5-cyano-6-[4-({[(3,4-difluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

Prepared according to method B starting from 1-(3,4-difluorophenyl)methanesulfonamide, made from the corresponding sulfonyl chloride in a similar manner to example 65b. Yield=16 mg (16%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.1 Hz), 1.53 - 1.70 (2H, m), 1.76 - 1.90 (2H, m), 2.47 - 2.54 (1H, m), 2.64 (3H, s), 3.15 (2H, app. t, J = 11.6 Hz), 4.25 (2H, q, J = 7.1 Hz), 4.47 - 4.57 (2H, m), 4.67 (2H, s), 7.08 - 7.18 (1H, m), 7.30 - 7.40 (1H, m), 7.41 - 7.53 (1H, m), 8.34 (1H, s), 11.42 - 12.03 (1H, m)
MS $^m/_z$: 507 (M+1).

Example 140

Ethyl 5-cyano-6-[3-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

1-[3-cyano-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]azetidine-3-carboxylic acid (43 mg, 0.150 mmol) was dissolved in 0.5 mL DCM followed by addition of TBTU (67 mg,0.21 mmol) and DIPEA (0.076 mL, 0.45 mmol). The solution was stirred at rt for 5 min followed by addition of 1-(4-methoxyphenyl)methanesulfonamide (80 mg, 0.180 mmol), which was prepared from the corresponding chloride in a similar fashion to example 109, dissolved in DCM. The reaction mixture was stirred for 18h followed by addition of TBTU(34 mg, 0.11

mmol) and DIPEA (0.152mL, 0.89 mmol). The reaction mix was stirred for 5 min foolowed by addition of 1-(4-methoxyphenyl)methanesulfonamide (27 mg, 0.060 mmol, 45 %) was dissolved in 0.2 mL DMF and added to the reaction mixture. Stirring at rt was continued for 16h. The solvents were removed in vacuo and the crude material was dissolved in 5 mL ethyl acetate followed by extraction with 2x5mL 1M NaHSO4 and 1x5 mL brine. The organic layer was isolated, dried over sodium sulphate, filtered and the solvents were removed in vacuo to give 0.136 g of crude material.

Purification was performed by reverse phase HPLC. Solvents used: A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=20 mL/min. just after in jection. Then changed to A/B/C 5:0:95. Increased to 50:0:50 over 30 min. in 9 equal steps. Then to 100:0:0 over 10 min. in 5 steps. Flow: 20 mL/min. Column: Kromasil C8, 250 mmx20 ID. The material stuck on the column and did not elute until A/B/C was 95/0/5 to 100/0/0.

The relevant fraction was evaporated and freeze dried, quantified (0.032 g) and 1 eq. 0.1 M NaOH was added. The material was freeze dried to give ethyl 5-cyano-6-[3-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate. Yield=34 mg (48%).

^{1}H NMR (400 MHz, DMSO-d6)δ 1.31 (3H, t, J = 7.2 Hz), 2.63 (3H, s), 3.14-3.23 (1H, m), 3.72 (3H, s), 4.21 (2H, s), 4.25 (2H, q, J = 7.2 Hz), 4.28-4.39 (4H, m), 6.79 (2H, br d, J = 8.6 Hz), 7.16 (2H, br d, J = 8.6 Hz), 8.28 (1H, s).

MS $^m/_z$: 473 (M+1)

Example 141

Cyclopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

1-{3-cyano-5-[(cyclopropyloxy)carbonyl]-6-methylpyridin-2-yl}piperidine-4-carboxylic acid (40 mg, 0.12 mmol), was dissolved in DCM followed by addition of TBTU (46.8 mg , 0.15 mmol)and DIPEA (0.11 mL, 0.61 mmol) after 10min. The reaction mixture was added to 1-(4-methylphenyl)methanesulfonamide (27 mg , 0.15 mmol) and was stirred over night. The solvents were removed in vacuo and the crude material was partitioned between EtOAc(5ml)/1 MKHSO4 (1mL). The organic layer was washed with water (1mL) and the solvents were removed in vacuo. The compound was purified by preparative HPLC to give

cyclopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate as a white solid. Yield=11 mg (97%)

^{1}H NMR (400 MHz, DMSO-d6) δ 0.71 - 0.85 (4H, m), 1.56 - 1.70 (2H, m), 1.78 - 1.90 (2H, m), 2.31 (3H, s), 2.55 - 2.62 (1H, m), 2.63 (3H, s), 3.07 - 3.20 (2H, m), 4.23 - 4.28 (1H, m), 4.48 - 4.60 (2H, m), 4.64 (2H, s), 7.17 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz), 8.30 (1H, s), 11.55 (1H, s)

MS $^m/_z$: 497(M+1).

Example 142

Ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-4-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to method B starting from 1-pyridin-4-ylmethanesulfonamide, which was prepared from the corresponding bromide in a similar fashion to example 109 step a. Yield=7 mg (8%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 6.9 Hz), 2.63 (3H, s), 3.39 - 3.49 (1H, m), 4.21 - 4.26 (2H, m), 4.28 - 4.55 (4H, m), 4.64 (2H, s), 7.28 - 7.42 (2H, m), 8.30 (1H, s), 8.48 - 8.62 (2H, m)

MS $^m/_z$: 444 (M+1).

Example 143

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

a) 1-[3-Cyano-6-(dimethylamino)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid

Ethyl 6-chloro-5-cyano-2-(dimethylamino)nicotinate (507 mg, 1.60 mmol) was dissolved in ethanol/water 1:1 followed by addition of azetidine-3-carboxylic acid (242 mg, 2.39 mmol) and TEA (0.644 mL, 4.80 mmol). The reaction mixture was heated in a microwave oven, single node heating, at 120°C for 20 min. The solvents were removed in vacuo and the residue was dissolved in in 15 mL DMSO. Some undissolved material was removed by filtration prior to purification by reverse phase HPLC.

A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to

flow=50 mL/min. continuous over 3 minutes after the injection. Then changed to A/B/C 5:0:95 and flow increased to 100 mL/min. Increased to 100:0:0 over 17 minutes in steps of 5% points. Column: Kromasil C8, 250 mmx50.8 ID.

This gave 1-[3-Cyano-6-(dimethylamino)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid. Yield = 0.064 g.(13%).

b)Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

1-[3-Cyano-6-(dimethylamino)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid (64 mg, 0.200 mmol) was dissolved in DCM and TBTU (96 mg, 0.300 mmol) and DIPEA (0.136 mL, 0.800mmol) were added. The mix was stirred for 5 minutes at r.t. before the addition of 1-phenylmethanesulfonamide (48 mg, 0.28 mol). The reaction mixture was stirred at r.t. for 16h.1-Phenylmethanesulfonamide (48 mg, 0.28 mol). ,TBTU (96 mg, 0.300 mmol) and DIPEA (0.136 mL, 0.800mmol) and stirring at r.t. was continued for 20h further. Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (93 mg, 0.20 mmol) was added and the mix was stirred at rt for 3.5 days (un-optimiz.). Thionyl chloride (0.044 mL, 0.600 mmol) was added and the reaction mixture was stirred for an additional 16h.

Purification was done by reverse phase HPLC. A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5. Start: A/B 5:95. Injected at flow=10 mL/min. Increased to flow=20 mL/min. 3 min. after injection. Then changed to A/B/C 5:0:95. Increased to 100:0 over 20 min., increasing with same interval each single minute. Flow: 20 mL/min. Column: Kromasil C8, 250 mmx20 ID. This gave a product that was only 71% pure. Rest was guanidine by-product.

Re-purification was done by reverse phase HPLC. A: MeCN, B: 0.1 M ammonium acetate/MeCN 95:5, C: 5% MeCN in 50 mM HCOOH/50 mM ammonium formiate. Start: A/B/C 5:95:0. Injected at flow=10 mL/min. Increased to flow=20 mL/min. 3 min. after in jection. Then changed to A/B/C 5:0:95. Increased to 100:0:0 over 20 min. in equal steps. Flow: 20 mL/min. Column: Kromasil C8, 250 mmx20 ID.

The above method gave ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate. Yield 11 mg. (12 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.40 (3H, m), 3.03 (6H, s), 3.00-3.06 (2H, m), 4.21-4.40(5H,m), 4.67 (2H, s), 7.33-7.45(5H, m), 8.10 (1H, s)

MS $^m/_z$: 472 (M+1)

Example 144

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate 1-oxide

a) Ethyl 6-chloro-5-cyano-2-methylnicotinate 1-oxide

Ethyl 6-chloro-5-cyano-2-methylnicotinate (1.00 g, 4.45 mmol) was dissolved in DCM (25mL) and cooled on an ice-bath. Urea hydrogen peroxide (2.09 g, 22.3 mmol) was charged and trifluoroaceticacid anhydride (3.11 mL, 22.3 mmol) was added droppwise during 2-3 minutes. The cooling bath was removed after 15min and the reaction mixture was stirred over night. Sodium Pyrosulphite 4.2g in 15 mL water was added and the reaction mixture was stirred for 3 min, followed by addition of DCM (5ml) and 1M KHSO4 (2ml) and stirring continued for 5 min. The aqueous layer was extracted three times with DCM and the combined organics were dried over sodium sulphate. Concentration yielded 900mg of a light yellow sticky solid. The crude material was purified by preparative HPLC, 50x300mm, C8, 10um to give ethyl 6-chloro-5-cyano-2-methylnicotinate 1-oxide. Yield=356mg (33%)

^{1}H-NMR (400 MHz, DMSO-d6) δ 1.34(3H, t, *J=7.1 Hz*), 2.68(3H, s), 4.36(2H, q, *J=7.1 Hz*), 8.25(1H, s)

b) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate 1-oxide

Ethyl 6-chloro-5-cyano-2-methylnicotinate 1-oxide (50 mg, 0.21 mmol) and *N*-(benzylsulfonyl)piperidine-4-carboxamide (59 mg, 0.21 mmol) were charged in a flask and dissolved in EtOH (2mL) where upon DIPEA (0.072 mL, 0.42 mmol) was added. The reaction mixture was concentrated in vacuo after 10min. The crude product was purified using preparative HPLC to give ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate 1-oxide. Yield=65mg:(64%)

^{1}H NMR (400 MHz, DMSO-d6) δ 1.32 (3H, t, *J=7.1Hz*), 1.70-1.84 (4H, m), 2.04-2.25(1H, m), 2.63(3H, s), 3.16-3.25(2H, m), 3.54(1H, br s), 3.71-3.80(2H, m), 4.26(2H, s), 4.30(2H, q, *J=7.1*), 7.21-7.30 (5H, m), 7.95 (1H, s)

MS $^m/_z$: 487(M+1).

Example 145

Ethyl 5-acetyl-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-2-methylnicotinate

a) Ethyl 5-acetyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate

3-Oxobutanamide (54.5 g, 539 mmol) was suspended in 400 mL EtOH. NaOEt/EtOH (210mL, 564 mmol, 21 %) was added dropwise and the reaction mixture was stirred at r.t. for 1h. Ethyl (2*E*)-2-acetyl-3-(dimethylamino)acrylate (100g, 513 mmol) dissolved in 400 mL EtOH was added dropwiseand the reaction mixture was stirred over night. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in water and acidified to pH 1 with concentrated HCl. The reaction was stirred for 2h followed by pH adjustement to ~ 8 using solid potassium carbonate and saturated sodium bicarbonate. The reaction mixture was extracted into EtOAc, and DCM, and each of the organics were washed with brine. The combined organics were dried over MgSO4, passed through asilica plug. The solvents were removed in vacuo and the remaining solids were triturated using 400 mL ether/hexane (1:1). This gave Ethyl 5-acetyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylateas a solid.

b) Ethyl 5-acetyl-6-chloro-2-methylnicotinate

Ethyl 5-acetyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.67g, 7.48 mmol) was dissolved in $POCl_3$ (13mL, 139 mmol) and the mixture was heated to 110°C and refluxed over night. The temnperature was lowered to r.t. followed by removal of $POCl_3$ under reduced pressure. The crude product was dissolved in DCM, washed with saturated $NaHCO_3$ twice followed by brine and water. The aqueous phase was extracted with DCM and the organic phases were combined and the solvents removed in vacuo. The crude material was co-concentrated from EtOH and DCM once each to give crude ethyl 5-acetyl-6-chloro-2-methylnicotinate material that was used imediately in the consecutive step.

c) 1-[3-acetyl-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid

Ethyl 5-acetyl-6-chloro-2-methylnicotinate (600mg, 2.11 mmol)) and piperidine-4-carboxylic acid (299 mg, 2.32 mmol) were dissolved in water (4ml) and MeCN (6ml) followed by addition of TEA (1.18mL, 8.44 mmol) was added. The reaction mixture was heated in a single node microwave oven for 20min at 120°C. The reaction mixture was diluted with DCM. Washed with 1%$KHSO_4$ twice, the combined aqueous phases were extracted with DCM and the combined organic phases were filtered through a phase separator and the solvents were removed in vacuo to give 1-[3-acetyl-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid as a crude product which was used immediately in the next step.Yield= 2.42 g (114%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.63 - 1.47 (2H, m), 1.92 - 1.78 (2H, m), 2.46 (3H, s), 2.61 (3H, s), 3.13 - 2.99 (2H, m), 3.87 - 3.74 (2H, m), 4.24 (2H, q, J = 7.0 Hz), 8.21 (1H, s)

d)Ethyl 5-acetyl-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-2-methylnicotinate

A solution of 1-[3-acetyl-5-(ethoxycarbonyl)-6-methylpyridin-2-yl]piperidine-4-carboxylic acid (872mg, 2.61 mmol)), DIPEA (2.27mL, 13.0 mmol) and TBTU (1.0 g, 3.11 mmol) dry DCM (15mL) was stirred for 15min at room-temperature followed by addition of 1-phenylmethanesulfonamide (536 mg, 3.13 mmol). The reaction mixture was stirred over night followed by addition of TBTU (100 mg, 0.31 mmol) and phenylmethanesulfonamide (53 mg, 0.31 mmol). The reaction mixture was then stirred for 5h followed by addition of DCM. The reaction mixture was washed twice with 1% KHSO4(aq). The aqueous phase was extracted with DCMx2 and the combined organic phases were passed through a phase separator and the solvents were removed *in vacuo*. The crude product was purified using preparative HPLC on a (Kromasil C8, 50.8 x 300mm), in order to avoid precipitation the the compound was loaded ont o the column using 5% acetonitrile/aqueous NH4OAc buffer pH 7. The product was eluted using a gradient of 40-10% acetonitrile/aqueous NH4OAc buffer pH 3. The fractions containing the product was concentrated *in vacuo*, dissolved in DCM and washed with water. The aqueous phase was extracted twice with DCM and the combinde organic phases were concentrated in vacuo to give ethyl 5-acetyl-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-2-methylnicotinate as a white/yellow solid. Yield=607 mg (48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz), 1.67 -1.85 (4H, m), 2.29-2.40(1H,m) 2.50 (3H, s), 2.70 (3H, s), 2.94- 3.04 (2H, m), 3.91-4.01 (2H, m), 4.32 (2H, q, J = 7.2 Hz), 4.64 (2H, s), 7.27- 7.41 (4H, m), 7.51 (1H, s), 8.38 (1H, s),
MS $^m/_z$: 488(M+1).

Example 146

ethyl 6-{4-{[(benzylsulfonyl)amino]carbonyl}-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-cyano-2-methylnicotinate

a) benzyl 4-{[(benzylsulfonyl)amino]carbonyl}-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate

1-[(benzyloxy)carbonyl]-4-[(*tert*-butoxycarbonyl)amino]piperidine-4-carboxylic acid (468mg, 1.24 mmol)), TBTU(440mg, 1.36 mmol) and DIPEA(0.3mL, 1.72 mmol) were dissolved in dry DCM (4mL) and stirred at rt for 1h. 1-Phenylmethanesulfonamide (217mg, 1.27 mmol) was added and the reaction mixture was stirred at r.t. for 17h. $NaHCO_3$(aq) was added and the mixture was extracted with DCM three times. The combined organic layers were run through a phase separator and the solvents were removed in vacuo. The crude product was purifed by prepHPLC, Column: Kromasil C8 10µm, 21.5x250mm, Mobilephase A: 100% can, Mobilephase B: 5% AcN, 95% NH_4AcO(aq) (pH7), Gradient: 20=>40% A over 35min, Flow: 25ml/min, UV: 220nm to give benzyl 4-{[(benzylsulfonyl)amino]carbonyl}-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate. Yield=297mg(45%).
LCMS:m/z: 530.4 (M-1).

b) *tert*-Butyl (4-{[(benzylsulfonyl)amino]carbonyl}piperidin-4-yl)carbamate

Benzyl 4-{[(benzylsulfonyl)amino]carbonyl}-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate (297mg, 0.56 mmol), $Pd(OH)_2$(96mg, 0.136 mmol, 20%wt) and ammonium formiate (544mg, 8.63 mmol) were suspended in MeOH(10mL) in a 20-mL microwave vial. The reaction mixture was heated to 120°C for 5min using microwave single node heating. $Pd(OH)_2$(50mg, 0.094 mmol, 20% wt) and ammonium formiate (300mg, 4.76 mmol) were added and the reaction mixture was heated to 120C for 5min. An additional amount of $Pd(OH)_2$(50mg, 0.094 mmol) and ammonium formiate(400mg, 6.34 mmol) were added and the reaction mixture was heated to 120C for 10min. The reaction mixture was filtered and evaporated. The crude product was used in the next step without further purification.
$LCMS^+/_z$: 398.2(M+1), 396.3(M-1).

c) ethyl 6-{4-{[(benzylsulfonyl)amino]carbonyl}-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-cyano-2-methylnicotinate

tert-Butyl (4-{[(benzylsulfonyl)amino]carbonyl}piperidin-4-yl)carbamate (107 mg, 0.27 mmol) and ethyl 6-chloro-5-cyano-2-methylnicotinate (124 mg, 0.55 mmol) were dissolved in EtOH(7mL) and H_2O(2mL) and DIPEA(1.3mL, 7.46 mmol) was added. The reaction mixture was heated to 120C for 5min using microwave singel node heating. $NaHCO_3$(aq) was added and the mixture was extracted three times with DCM. The combined organic layer was run through a phase separator and the solvents were removed in vacuo. The crude product was purified by prepHPLC Column: Kromasil C8 10µm, 21.5x250mm, Mobilephase A: 100%

AcN, Mobilephase B: 5% AcN, 95% NH_4AcO(aq) (pH7),Gradient: 25=>50% A over 35min, Flow: 25ml/min
UV: 296nm to give ethyl 6-{4-{[(benzylsulfonyl)amino]carbonyl}-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-cyano-2-methylnicotinate. Yield=9 mg(3%).
LCMS$^+/_z$: 586.4 (M+1), 584.4(M-1).

Example 147

ethyl 6-(4-amino-4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

Ethyl 6-{4-{[(benzylsulfonyl)amino]carbonyl}-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-cyano-2-methylnicotinate (7.6mg, 0.013 mmol) was dissolved in DCM(5mL) and TFA(2mL) was added. The reaction mixture was stirred at r.t. for 1h followed by removal of the solvents in vacuo. The product was redissolved in AcN/H_2O and freezedried yielding ethyl 6-(4-amino-4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate trifluoroacetate. Yield=8mg(100%).
LCMS$m/_z$: 486.3(M+1), 484.3(M-1).

Further Examples

General Experimental Procedure

Mass spectra was recorded on a Finnigan LCQ Duo ion trap mass spectrometer equipped with an electrospray interface (LC-ms) or LC-ms system consisting of a Waters ZQ using a LC-Agilent 1100 LC system. ^1H NMR measurements were performed on a Varian Mercury VX 400 spectrometer, operating at a 1H frequency of 400 and Varian UNITY plus 400,500 and 600 spectrometers, operating at 1H frequencies of 400,500 and 600 respectively. Chemical shifts are given in ppm with the solvent as internal standard. Protones on heteroatoms such as NH and OH protons are only reported when detected in NMR and can therfore be missing. Chromatography was performed using Biotage silica gel 40S, 40M, 12i or Merck silica gel 60 (0.063-0.200mm). Flashchromatography was performed using either standard glass- or plastic-columns column or on a Biotage Horizon system. HPLC separations were performed on a Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm or on a Waters Delta Prep Systems using Kromasil C8, 10 µm columns.

The purification system and LC-MS system used in Method A´ to E´ below was Waters Fraction Lynx II Purification System: Column: Sunfire Prep C18, 5 µm OBD, 19 x 100 mm column. Gradient 5-95 % CH_3CN in 0.1 mM HCOOH (pH=3). MS triggered fraction collection was used. Mass spectra were recorded on either Micromass ZQ single quadropole or a Micromass quattro micro, both equipped with a pneumatically assisted electrospray interface.

Reactions performed in a microwave reactor were performed in a Personal Chemistry Smith Creator, Smith synthesizer or an Emrys Optimizer.

List of used abbreviations:

Abbreviation	Explanation
AcOH	Acetic acid
aq	Aqueous
br	Broad
Brine	A saturated solution of sodium chloride in water
BSA	Bovine Serum Albumine
$(Boc)_2O$	di-tert-butyl dicarbonate
BuLi	Butyl lithium
CDI	Carbonyldiimidazole
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	Dimethylsulphoxide
EDCI	N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride

EtOAc	Ethyl acetate
EtOH	Ethanol
HEPES	[4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HFA	Hydrofluoroalkanes
HOAc	Acetic acid
HOBT	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
Hz	Hertz
J	Coupling constant
LDA	Litiumdiisopropyl amide
m	Multiplet
Me	methyl
MHz	Megahertz
mL	Millilitre
MS	Mass spectra
NCS	N-chlorosuccinimide
OAc	acetate
^{i}PrOAc	iso-propyl acetate
q	Quartet
r.t	Room temperature
s	Singlet
t	triplet
TB	Tyrodes Buffer
TBME	tert-butylmethyl ether
TBTU	N-[(1H-1,2,3-benzotriazol-1-yloxy)(dimethylamino)methylene]-N-methylmethanaminium tetrafluoroborate
TEA	Triethylamine
Tf	trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TMEDA	N,N,N',N'-tetramethylethylendiamine
Ts	p-toluenesulfonyl

Synthesis of sulfone amides

The synthesis of the sulfonamides used in the examples below was made with one of the three methods described below:

i) By reacting the corresponding sulfonyl chloride with ammonia in THF or MeOH or by treatment with ammonium hydroxide in methylene chloride. The sulfonamides obtained was used without further purification.

ii) By essentially following the procedure described by Seto, T. et. al. in J. Organic Chemistry, Vol 68, No 10 (2003), pp. 4123-4125.

or

iii) By essentially following the procedure described by Wang, Z et. al. in Tetrahedron Letters, Vol 43 (2002), pp 8479-8483.

Synthesis of examples

The following general procedures (i.e. Method A′ to E′) were used to prepare some of the examples below and are referred to in each specific example.

Method A′: examplified by the procedure from Example 10

DIPEA (64 mg, 0.5 mmol) was added to a solution of 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic (35.3 mg, 0.1mmol) and TBTU (38.5 mg, 0.12mmol) in DCM (5mL) and the mixture was stirred for 30min at r.t before 1-(2-fluorophenyl)methanesulfonamide (23 mg, 0.12mmol) dissolved in DCM (1 mL) was added. The reaction was allowed to stir over night. LC-MS showed that starting material was left and more TBTU (19 mg, 0.06mmol) and DIPEA (26 mg, 0.2mmol) were added to the mixture and

the stirring was continued for another 2h. The reaction mixture was washed with 1%$KHSO_4$, the aqueous phase was extracted with DCM (1ml) and the combined organic phases passed through a phase separator and evaporated in a vaccum centrifuge. The crude product obtained was purified by HPLC (See General experimental procedure) to give ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate.Yield: 41 mg (78 %).

Method B′ : examplified by the procedure from Example 42

DIPEA (128 mg, 1.0 mmol) was added to a solution of {1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}acetic acid (74.2 mg, 0.2mmol) and TBTU (77 mg, 0.24 mmol) in DCM (7mL) and the mixture was stirred for 30min at r.t before 1-phenylmethanesulfonamide (41 mg, 0.24 mmol) dissolved in DCM (1 mL) was added and the reaction was left over night. The reaction mixture was washed with 1% $KHSO_4$, the aqueous phase was extracted with DCM and the combined organic phases passed through a phase separator and evaporated in vaccum centrifuge. The crude product obtained was purified by HPLC (See General experimental procedure) to give ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}pyrrolidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 88 mg (84 %).

Method C′ : examplified by the procedure from Example 55

DIPEA (43 mg, 0.3 mmol) and TBTU (64 mg, 0.20 mmol) was added to a solution of 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid (74.2 mg, 0.2 mmol) in DMF and the mixture was stirred for 2 hours at r.t before it was added to 1-(4-fluorophenyl)methanesulfonamide (38 mg, 0.22 mmol) dissolved in DMF. The reaction mixture was stirred over night and passed through SCX-2 ion exchange column. The crude product obtained was purified by HPLC (See General experimental procedure) to give ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 4.3 mg (4%).

Method D′: examplified by the procedure from Example 45

CDI (26 mg, 0.16 mmol) was added to a solution of 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid (51 mg, 0,15 mmol) (gas evolution) in CH_3CN and the mixture was heated to 50°C for 2 hours. The above mixture was then added to a soultion of 1-(4-fluorophenyl)methanesulfonamide (28 mg, 0.15 mmol) and DBU (23 mg, 0.15 mmol) in CH3CN and the reaction was stirred at r.t over night. Purification by HPLC (See experimental procedure) gave ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate.

Method E': examplified by the procedure from Example 75

DIPEA (38 mg, 0.3 mmol) was added to a solution of 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic (35.3 mg, 0.1mmol) and TBTU (38.5 mg, 0.12 mmol) in DCM (2mL) and the mixture was stirred for 10 min at r.t before 1-(2-fluorophenyl)methanesulfonamide (19 mg, 0.10mmol) was added. The reaction was allowed to stir over night.. The reaction mixture was washed with 1M $KHSO_4$ and the organic phases passed through a phase separator and evaporated in a vaccum centrifuge. The crude product obtained was purified by HPLC (See General experimental procedure) to give ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 13 mg (25 %).

Example 148

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-(difluoromethyl)nicotinate

(a) ethyl 2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate

Ethyl 2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (2.0 g, 11.04 mmol) (Sobczak, A et al, Synth. Commun, Vol. 35, No. 23, 2005, pp2993-3001) was added to a solution of 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ^4-sulfanyl)ethanamine (7.82 g, 22.08 mmol) in CH_3CN under an atmosphere of nitrogen. The reaction was refluxed over night after which further 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-λ^4-sulfanyl)ethanamine (2.73 g, 7.7 mmol) was added and the stirring was continued until all startingmaterial was consumed. The

reaction was diluted with diethyl eter, filtered to remove black solids, washed with water and $NaHCO_3$ (aq,sat). Both phases were filtered again to remove more of black solids. The aqueous phase was extracted with diethyl ether (2 times) and the combined organic phase was dried ($MgSO_4$), filtered and concentrated and slurried in diethyl ether to remove yellow impurities. Drying of the remaining white solid gave ethyl 2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate. Yield: 370 mg (14 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J=7.2 Hz), 4.36 (2H, q, J = 7.2 Hz), 6.69 (1H, d, J= 10 Hz), 7.56 (1H, t, J= 54 Hz), 7.99 81H, d, J = 10 Hz).

(b) ethyl 5-chloro-2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate

NCS (270 mg, 2.02 mmol) dissolved in DMF (2 mL) was added to a solution of ethyl 2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (365 mg, 1.44 mmol) and the reaction was heated to 100 °C over night. Since staring material still remained further aliquots of NCS (135 mg, 1.01 mmol and 5 hours later 270 mg, 2.02 mmol) was added and the heating was continued until the the startingmaterial had dissappeared. The reaction was diluted with DCM and washed with water and Brine. The water phase was extracted twice with DCM and the combined organic phase was passed through a phase separator and evaporated. Purification by flash chromatography (Horizon Flash 40+M, Eluent: a gradient of EtOAc/ Heptane from 50 to 100 % EtOAc was used)) gave ethyl 5-chloro-2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate as a yellow oil which was used in the next step without further analysis or purification. Yield: 88 mg (15 %).

(c) ethyl 5,6-dichloro-2-(difluoromethyl)nicotinate

Oxalylchloride (0.1 mL, 1.18 mmol) together with DMF (0.1 mL) was added to a solution of ethyl 5-chloro-2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (85.5 mg, 0.217 mmol) in DCM and the mixture was heted to 42 °C for 3 hours. No product could be detected and therfore another 0.1 mL (1.18 mmol) oxalylchloride was added and the strirring was continued at 42 °C over night. He reaction was diluted with DCM and quenched by poring it on an ice/water mixture. The phases was separeted and the organic phase was awshed with NaHCO3 (aq, sat) and Brine. The combined water phase was extracted with DCM and the combined organic phase was filtered through a phase separator and evaporated. The residue was co-concentrated twice with DCM to give ethyl 5,6-dichloro-2-(difluoromethyl)nicotinate

as a yellow oil which was used in the next step without further purification. Yield: 113.5 mg (51 %).

(d) tert-butyl 4-[(benzylsulfonyl)carbamoyl]piperidine-1-carboxylate

Triethylamine (591 g, 5840 mmol) was added to a stirred suspension of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (448 g, 1954 mmol), LiCl (23.1 g, 545 mmol) and TBTU (657 g, 2046 mmol) in THF (3000 mL) under an atmosphere of nitrogen at r.t.. A solution of 1-phenylmethanesulfonamide (352 g in 1300 mL THF, 2056 mmol) was added after 1.5 hours and the stirring was continued over night . The solvent was removed *in vaccuo* to give a thick grey-beige slurry (volume about 2500 mL). EtOAc (3500 mL) was added followed by an aqueous solution of HCl (1960 mL 3.6 M HCl and 1960 mL water). The water phase was removed and the organic phase was washed with 2 x 1500 mL 1 M HCl. The organic phase was cooled to 0°C which gave a precipitate of HOBT that was filtered off. Most of the solvent was removed *in vaccuo* to give a thick grey-white slurry. EtOH (50 %, 4000 mL) was added and the slurry was stirred for 1.5 hours. The precipitated product was filtered off , washed with 50 % EtOH (500 mL + 2 x 1500 mL) and dried in a vaccum oven at 25 °C to give tert-butyl 4-[(benzylsulfonyl)carbamoyl]piperidine-1-carboxylate as a white solid. Yield 584 g (78 %).

(e) N-(benzylsulfonyl)piperidine-4-carboxamide

tert-Butyl 4-[(benzylsulfonyl)carbamoyl]piperidine-1-carboxylate (583 g, 1524 mmol) was suspended in formic acid (3000 mL) under a nitrogen atmosphere and the reaction was stirred for 20 minutes. The reaction was foaming due to the gas evolution and formic acid (500 mL) was used to wash down the foam from the reaction vessel walls. After 2 hours the foaming had stopped and the reaction was clear with a few solids left. The reaction was stirred over night and 2500 mL of formic acid was removed in vaccuo. Water (1000 mL) was added and the reaction was filtered. The clear solution was evaporated and water (3000 mL) was added. A saturated ammonium hydroxide solution in water was used (totally 390 mL was added and the pH was going from 3.10 to 6.10) to neutralize the acidic solution and at the endpoint (pH=6.10) a heavy precipitate of the product was formed. The mixture was stirred over night and the precipitate was filtered off and washed with water (1000 mL). Drying in a vaccum

oven at 25°C gave N-(benzylsulfonyl)piperidine-4-carboxamide as a white powder. Yield 372.4 g (87%).

(f) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-(difluoromethyl)nicotinate

TEA (149 µL, 1.07 mmol) was added to a solution of ethyl 5,6-dichloro-2-(difluoromethyl)nicotinate (113 mg,0.214 mmol)) and *N*-(benzylsulfonyl)piperidine-4-carboxamide (66 mg, 0.24 mmol) in CH_3CN (3 mL) and water (2 mL) .The reaction was heated in a single node microwave at 120°C over 20 minutes. The solvents were removed *in vacuo* and the crude mixture was diluted with DCM and washed twice with 1% $KHSO_4$(aq). The combined aqueous phase was extracted with DCM and the combined organic phases were passed through a phaseseparator followed by removal of solvents in vacuo.
The crude product was purified using preparative HPLC on a (Kromasil C8, 50.8 x 300 mm), the compound was loaded onto the column using 5% acetonitrile/aqueous NH4OAc buffer pH 7 and then eluted using a gradient of 30-100% acetonitrile/aqueous NH_4OAc buffer pH 3.

Product-fractions were combined and the solvent was removed *in vacuo*, and triturated with DCM followed by filtration. The solvents were removed *in vacuo* to give ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-(difluoromethyl)nicotinate as a white solid. Yield: 13 mg (11 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 7.1 Hz), 1.73-1.91(4H, m), 2.27-2.42(1H, m), 2.87-3.05(2H, m), 4.19-4.30(2H,m), 4.30-4.41(2H, m), 4.67 (2H, s), 7.29 - 7.43 (5H, m), 7.48 - 7.54 (1H, m), 8.16 (1H, s)

Example 149

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

(a) ethyl 5-cyano-2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate

1,1-Dimethoxy-N,N-dimethylmethanamine (4.8 mL, 36.1 mmol) was added to ethyl 4,4-difluoro-3-oxobutanoate (5.0 g, 30.1 mmol) (exotermic reaction). The orange solution was

stirred at r.t over night , concentrated and co-evaporated with toluene. The residue was taken up in EtOH (99.5 %, 10 mL) to give a red solution. Freshly prepared NaOEt (1M, 30 mL) was added to a solution of 2-cyanoacetamide (2.53 g, 30.1 mmol) in EtOH (99.5 %, 30 mL) and the reaction was stirred at r.t for 1 hour and the above red solution was added dropwise. The red suspension formed was stirred over night and HOAc (6 mL) was added and the solution became clear. The solution was concentrated and slurried in water (50 mL) and stirred for 1 hour after which the precipitae was filtered off and dried in air to give ethyl 5-cyano-2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate as a brown solid. Yield: 3.03 g (41 %).

1H-NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J=7.2 Hz), 4.28 (2H, q, J = 7.2 Hz), 7.48 (1H, t, J= 52.5 Hz, F-coupling), 8.58 (1H, s).

(b) ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinate

Oxalylchloride (5.3 mL, 62.6 mmol) followed by DMF (0.097 mL) was added to a slurry of ethyl 5-cyano-2-(difluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (3 g, 12.5 mmol) in DCM (45 mL) and the reaction was heated to 50 °C for a few hours, more oxalylchloride was added (1 mL , 11.8 mmol) and DMF (0.2 mL) was added twice with a few hours inbetween and the heating was continued at reflux over night. The reaction mixture was evaporated and the residue was taken up in DCM and washed with water and $NaHCO_3$ (aq,sat), The aqueous phase was extracted with DCM (twice) and the combined organic phase was concentrated and purified by flash chromatography (Horizon, Eluent a gardient of Heptane/EtOAc 7/1 to 100 % EtOAc was used) to give ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinate as a yellow oil. Yield: 2.0 g (60 %).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.34 (3H, t, J = 7.0), 4.37 (2H, q, J= 7.0 Hz), 7.46 (1H, t, J = 53.2 Hz), 8.99 (1H, s).

(c) ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

TEA (0.4 mL, 2.89 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinate (200 mg, 0.721 mmol) and N-(benzylsulfonyl)piperidine-4-carboxamide (224 mg, 0.793 mmol) in water (2.5 mL) and EtOH (2 mL). The mixture was

heated in a single-node microwave oven at 120 oC for 20 minutes, The solvents were evaporated and the residue was taken up in DCM and washed with 1 % $KHSO_4$ (twice). The combined aqueous phase was extracted with DCM (twice) and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 40 % CH_3CN to 100 % CH_3CN/(50 mM HCOOH and 50 mM NH_4OOCH, pH=3) gave ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate as a white solid. Yield 250 mg (68%).

1H NMR (400MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.4 Hz), 1.73 - 1.59 (2H, m), 1.91 - 1.81 (2H, m), 2.61 (1H, m), 3.27 - 3.15 (2H, m), 4.28 (2H, q, J = 7.4 Hz), 4.61 - 4.51 (2H, m), 4.69 (2H, s), 7.33 - 7.22 (2H, m), 7.44 - 7.34 (3H, m), 7.53 (1H, s), 8.50 (1H, s), 11.61 (1H, s)

Example 150

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

(a) ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate

Oxalylchloride (12.20 g, 96.1 mmol) and DMF (0.744 mL) were added to a solution of ethyl 5-cyano-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3-carboxylate (5 g, 19.22 mmol) (prepared essentially according to the Method D´escribed in Mosti, L et al, Farmaco, Vol 47, No 4, 1992, pp427-437) and the reaction was heted to 50°C over night. The reaction was evaporated and the crude was dissolved in EtOAc and water. The phases was separated and the organic phase was washed with Brine and $NaHCO_3$ (aq,sat). The aqueous phase was extracted with EtOAc (3 times) and the combined organic phase was dried (Na2CO3), filtered and concentrated to give ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate as a brown solid which was used without further purification. Yield: 5.206 g (95 %).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.31 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 6.9 Hz, 2H), 9.07 (s, 1H)

(b) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

TEA (142 mg, 1.41 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate (140 mg, 0.352 mmol) and N-(benzylsulfonyl)piperidine-4-carboxamide (109 mg, 0.387 mmol) in water (2 mL) and EtOH (2.5 mL).). The mixture was heated in a single-node microwave oven at 120 oC for 20 minutes, The solvents were evaporated and the residue was taken up in DCM and washed with 1 % KHSO4 (twice). The combined aqueous phase was extracted with DCM (twice) and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 30 % CH_3CN to 100 % CH_3CN/(50 mM HCOOH and 50 mM NH_4OOCH, pH=3) gave ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate as a white solid. Yield: 107 mg (58 %).
^{1}H NMR (400MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.5 Hz), 1.74 - 1.58 (2H, m), 1.91 - 1.79 (2H, m), 2.65 - 2.54 (1H, m), 3.27 - 3.15 (2H, m), 4.28 (2H, q, J = 7.5 Hz), 4.55 - 4.46 (2H, m), 4.68 (2H, s), 7.33 - 7.23 (2H, m), 7.47 - 7.35 (3H, m), 8.54 (1H, s), 11.61 (1H, s).

Example 151

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

(a) 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid

$(Boc)_2O$ (25.535 g, 117 mmol) dissolved in MeOH (70 mL) was added dropwise during 20 minutes to a stirred slurry of azetidine-3-carboxylic acid (10.11 g, 100 mmol) and Et_3N (27.8 mL, 200 mmol) in MeOH (105 mL) at r.t (mildly exotermic reaction) and the mixture was stirred over night (18 hours). The reaction was evaporated to dryness and THF (120 mL) was added and evapoprated to give crude 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid which was used without further purification in the next step. Yield: 25.89 g (128 %)
^{1}H NMR (400MHz, $CDCl_3$) δ 1.43 (9H, s), 3.21-3.34 (1H, m), 4.00-4.13 (4H, m).

(b) *tert*-butyl 3-[(benzylsulfonyl)carbamoyl]azetidine-1-carboxylate

TBTU (33.71 g, 105 mmol) and TEA (30.3 g, 300 mmol) was added to a solution of 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid from above (25.89 g, assumed to contain 100

mmol) and the reaction was stirred at r.t for 30 minutes. 1-phenylmethanesulfonamide (17.97 g, 105 mmol) and LiCl (1.844 g, 43.5 mmol) was added and the stirring was continued at r.t over night (23 hours). The reaction was concentrated to about 1/3 was left and EtOAc (500 mL) was added and the organic phase was washed with 2 M HCl (1 x 150 mL, 2 x 50 mL), water (2 x 50 mL). Drying ($MgSO_4$), filtration and evaporation of the solvent gave a brown powder (48. 6 g). The powder was slurried in 150 mL TBME and stirred 3 hours. The solids was filtered off and washed with TBME (40 mL). This procedure was repeated twice with 100 mL TBME (washing with 25 mL) to give a brownish powder (33 g) still containing some HOBT. The powder was dissolved in about 100 mL warm EtOH and water (130 mL) was added to induce a crystallisation of the product. The crystals was filtered off and dried to give pure tert-butyl 3-[(benzylsulfonyl)carbamoyl]azetidine-1-carboxylate as an offwhite powder. Yield: 25.4 g (71%).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.39 (9H, s), 3.30 (1H, m, overlapping with the watersignal in DMSO), 3.78-3.95 84H, m), 4.73 (2H, s), 7.28-7.34 (2H, m), 7.36-7.41 (3H, m), 11.71 (1H, br s).

MS $^m/_z$: 353 (M-1).

(c) N-(benzylsulfonyl)azetidine-3-carboxamide

tert-butyl 3-[(benzylsulfonyl)carbamoyl]azetidine-1-carboxylate (25.4 g, 71.7 mmol) was added to HCOOH (300 mL) at r.t and the reaction was stirred over night (22 hours). The formic acid was removed in vaccuo, water (40 mL) was added and removed in vaccuo. Water (130 mL) was added to the residue followed by NH4OH (aq) until pH reached 7.4 when a crystallization started. The crystals was filtered off and dried to give pure N-(benzylsulfonyl)azetidine-3-carboxamide as a white solid. Yield 15.73 g (86 %).

^{1}H NMR (400MHz, DMSO-d_6) δ 3.22 (1H, m), 3.87-3.96 (4H, m), 4.28 (2H, s), 7.20-7.32 (5H, m).

MS $^m/_z$: 255 (M+1)

(d) Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

TEA (291 mg, 2.88 mmol) was added to a solution of ethyl ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinate (200 mg, 0.721 mmol) and N-(benzylsulfonyl)azetidine-3-carboxamide (201 mg, 0.793 mmol) in water (2 mL) and EtOH (2.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 20 minutes, The solvents were evaporated and the residue was taken up in DCM and washed with 1 % $KHSO_4$ (twice). The combined aqueous phase was extracted with DCM (twice) and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 40 % CH_3CN to 100 % CH_3CN/(50 mM HCOOH and 50 mM NH_4OOCH, pH=3) gave ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate as a white solid. Yield 264 mg (72 %).
^{1}H NMR (400MHz, DMSO-d_6) d 1.30 (3H, t, J = 7.3 Hz), 3.64 - 3.53 (1H, m), 4.27 (2H, q, J = 6.9 Hz), 4.53 - 4.31 (4H, m), 4.75 (2H, s), 7.40 - 7.30 (5H, m), 7.40 (1H, t, J = 53.6 Hz), 8.47 (1H, s), 11.81 (1H, s)
MS $^m/_z$: 478 (M+1)

Example 152

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

(a) ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate

Oxalylchloride (8.13 mL, 96.1 mmol) and DMF (0.744 mL, 9.61 mmol) were added to a solution of ethyl 5-cyano-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridine-3-carboxylate (5.0 g, 19.22 mmol, prepared essentially according to the procedure described by Mosti L, et. al. Farmaco, Vol 47, No 4, 1992, pp. 427-437) and the reaction was heted to reflux over night.The solvent was evaporated and the residue was dissolved in EtOAc/water. The phases were separated and the organic phase was awshed with Brine and NaHCO3 (aq) (twice). The aqueous phase was extracted with EtOAc (three times) and the combinec organic phases was dried (Na_2CO_3), filtered and concentrated to give ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate which was used without further purification. Yield: 5.21 g (95%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J= 7 Hz), 4.38(2H, q, J= 7 Hz), 9.07 (1H, s).

(b) Ethyl 6-(3-{[(benzylsulfonyl)amino]carbo nyl}azetidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

TEA (142 mg, 1.41 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate (140 mg, 0.352 mmol) and N-(benzylsulfonyl)azetidine-3-carboxamide (98.4 mg, 0.387 mmol) in water (2 mL) and EtOH (2.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 20 minutes. The reaction was filtered to remove a precipitate and the solvents were evaporated. The residue was taken up in DCM and washed with 1 % $KHSO_4$ (twice). The combined aqueous phase was extracted with DCM (twice) and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 30 % CH_3CN to 100 % CH_3CN/(0.1 % HCOOH(aq)) gave ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate as a white solid. Yield 102 mg (58 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.3 Hz), 3.63 - 3.52 (1H, m), 4.27 (2H, q, J = 7.3 Hz), 4.52 - 4.31 (4H, m), 4.74 (2H, s), 8.50 (1H, s), 11.80 (1H, s).
MS $^m/_z$: 496 (M+1)

Example 153

Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinate

(a) ethyl 5-cyano-2-(fluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate

1,1-dimethoxy-N,N-dimethylmethanamine (4.83 g, 40.5 mmol) was added to ethyl 4-fluoro-3-oxobutanoate (5.0 g, 33.75 mmol) at r.t (exotermic reaction) and the mixture was stirred over night, concentrated and co-evaporated with toluene. EtOH (99.5 %, 10 mL) was added to give a red solution. Freshly prepared sodium ethoxide 1M solution (34.5 mL, 2.35 g, 34.5 mmol) was added to a solution of 2-cyanoacetamide (3.12 g, 37.13 mmol) in EtOH (99.5 %, 30 mL) and after stirring at r.t for 35 minutes the red solution from above was added dropwise and the stirring continued over over night. AcOH (6 mL) was carefully added (exotermic reaction) and the precipitate formed was filtered and washed with diethyl eter. Drying

afforded ethyl 5-cyano-2-(fluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate as a beige solid. Yield 4.42 g (56 %).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.24 (3H, t, J = 7.2 Hz), 4.12 (2H, q, J = 6.9 Hz), 5.42 (2H, d, J = 47.5 Hz), 7.96 (1H, s).
MS $^m/_z$: 225 (M+1).

(b) ethyl 6-chloro-5-cyano-2-(fluoromethyl)nicotinate

Oxalylchloride (5.49 mL, 64.9 mmol) and DMF (0.5 mL, 6.5 mmol) were added to a solution of ethyl 5-cyano-2-(fluoromethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (3.0 g, 12.98 mmol) in DCM (120 mL) and the mixture was heated to reflux for 6 hours. The solvent was evaporated and the residue was dissolved in EtOAc/water. The phases were separated and the organic phase was awshed with Brine and NaHCO3 (aq). The aqoeous phase was extracted with EtOAc (twice) and the combined organic phase was concentrated to give ethyl 6-chloro-5-cyano-2-(fluoromethyl)nicotinate as a beige solid which was used without further purification. Yield: 2.92 g (90 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (t, J = 7.1 Hz, 3H), 4.34 (q, J = 7.1 Hz, 2H), 5.88 (s, 1H), 5.77 (s, 1H), 8.89 (s, 1H)
MS $^m/_z$: 243 (M+1)

(c) Ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinate

TEA (326 mg, 3.23mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(fluoromethyl)nicotinate (200mg, 0.81 mmol) and N-(benzylsulfonyl)piperidine-4-carboxamide (251 mg, 0.89 mmol) in CH_3CN (1.5 mL) and 95 % EtOH (2.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 20 minutes. The solvent was evaporated and the residue was taken up in DCM and washed with 1 % KHSO4 (twice). The combined aqueous phase was extracted with DCM and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 40 % CH3CN to 100 % CH3CN/(0.1 % HCOOH(aq)) gave ethyl 6-(4-

{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinaten as a beige solid. Yield: 257 mg (65 %).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.71 - 1.56 (2H, m), 1.89 - 1.79 (2H, m), 2.65 - 2.54 (1H, m), 3.24 - 3.12 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.64 - 4.53 (2H, m), 4.68 (2H, s), 5.63 (1H, s), 5.75 (1H, s), 7.33 - 7.23 (2H, m), 7.44 - 7.34 (3H, m), 8.40 (1H, s), 11.60 (1H, s).

MS $^m/_z$: 489 (M+1)

Example 154

Ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinate

TEA (326 mg, 3.23mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(fluoromethyl)nicotinate (200mg, 0.81 mmol) and N-(benzylsulfonyl)azetidine-3-carboxamide (225 mg, 0.89 mmol) in CH3CN (1.5 mL) and 95 % EtOH (2.5 mL). The mixture was heated in a single-node microwave oven at 120 oC for 20 minutes. The solvent was evaporated and the residue was taken up in DCM and washed with 1 % KHSO4. The combined aqueous phase was extracted with DCM and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 40 % CH3CN to 100 % CH3CN/(0.1 % HCOOH(aq)) gave ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(fluoromethyl)nicotinate as a beige solid.Yield 221 mg (59 %)

^{1}H NMR (400MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.62 - 3.51 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.39 - 4.29 (2H, m), 4.51 - 4.39 (2H, m), 4.74 (2H, s), 5.61 (1H, s), 5.73 (1H, s), 7.42 - 7.29 (5H, m), 8.38 (1H, s), 11.81 (1H, s).

MS $^m/_z$: 461 (M+1).

Example 155

Ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

(a) 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid

TEA (423 mg, 4.18 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinat (290 mg, 1.05 mmol) and piperidine-4-carboxylic acid (148 mg, 1.15 mmol) in water/EtOH (4.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 10 minutes. The solvent was evaporated and the residue was taken up in DCM and washed with 1 % KHSO4. The combined aqueous phase was extracted with DCM (twice) and the combined organic phase was filtered through a phase separator and concentrated to give 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid as a white solid which was used without further purification. Yield: 356 mg (94 %).

1H-NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J= 7.2 Hz), 1.84-1.97 (2H, m), 2.08-2.17 (2H, m), 2.69-2.79 (1H, m), 3.37-3.47 (2H, m), 4.37 (2H, q, J=7.2 Hz), 4.61-4.70 (2H, m), 7.39 (1H, t, CHF_2), 8.43 (1H, s).

MS $^m/z$: 354 (M +1)

(b) Ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

DIPEA (64 mg, 0.5 mmol) was added to a solution of 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic (35.3 mg, 0.1mmol) and TBTU (38.5 mg, 0.12mmol) in DCM (5mL) and the mixture was stirred for 30min at r.t before 1-(4-methylcyclohexyl)methanesulfonamide (23 mg, 0.12mmol) dissolved in DCM (1 mL) was added. The reaction was allowed to stir over night. LC-MS showed that starting material was left so more TBTU (19 mg, 0.06mmol) and DIPEA (26 mg, 0.2mmol) were added to the mixtureand the stirring was continued for another 2h. The reaction mixture was washed with 1%KHSO4, the aqueous phase was extracted with DCM (1ml) and the combined organic phases passed through a phase separator and evaporated in vaccum centrifuge. The crude product obtained was purified by HPLC (Kromasil C_8, using a gradient of 20 % to 100 % CH_3CN/0.2 % HOAc(aq)) to give ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate as a white solid.Yield: 22mg (40 %).

^{1}H NMR (400MHz, $CDCL_3$-d_6) δ 8.61 (1H, s), 8.42 (1H, s), 7.36 (1H, t, J = 54.3 Hz), 4.75 (2H, m), 4.35 (2H, q, J = 7.3 Hz), 3.46 (1H, m), 3.38 - 3.22 (3H, m), 2.59 (1H, m), 2.30 - 2.18

(1H, m), 2.10 - 1.97 (2H, m), 1.96 - 1.79 (3H, m), 1.75 - 1.47 (6H, m), 1.37 (3H, t, J = 7.2 Hz), 1.22 - 1.04 (2H, m), 0.92 - 0.83 (3H, m).
MS ^{m}/z: 527 (M+1)

Example 156

Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

(a) 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid

TEA (423 mg, 4.18 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinat (290 mg, 1.05 mmol) and azetidine-3-carboxylic acid (116 mg, 1.15 mmol) in 95% EtOH (4.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 10 minutes. The solvent was evaporated and the residue was taken up in DCM and washed with 1 % KHSO4. The combined aqueous phase was extracted with DCM (twice) and the combined organic phase was filtered through a phase separator and concentrated to give 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid acid as a white solid which was used without further purification. Yield: 359 mg (101 %).
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J= 7.1 Hz), 3.62-3.72 (1H, m), 4.36 (2H, q, J=7.1 Hz), 4.63-4.75 (4H, m), 7.34 (1H, t, J= 54.2 Hz, CHF_2), 8.36 (1H, s).
MS ^{m}/z: 326 (M +1)

(b) Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinat

DIPEA (64 mg, 0.5 mmol) was added to a solution of 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid (32.5 mg, 0.1mmol) and TBTU (38.5 mg, 0.12mmol) in DCM (5mL) and the mixture was stirred for 30min at r.t before 1-(2-fluorophenyl)methanesulfonamide (23 mg, 0.12mmol) dissolved in DCM (1 mL) was added. The reaction was allowed to stir over night. LC-MS showed that starting material was left so more TBTU (19 mg, 0.06mmol) and DIPEA (26 mg, 0.2mmol) were added to the mixtureand the stirring was continued for another 2h. The reaction mixture was washed with 1%KHSO4,

the aqueous phase was extracted with DCM (1ml) and the combined organic phases passed through a phase separator and evaporated in vaccum centrifuge. The crude product obtained was purified by HPLC (Kromasil C_8, using a gradient of 20 % to 100 % CH_3CN/0.2 % HOAc(aq)) to give ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate as a white solid. Yield: 42mg (83 %).

^{1}H NMR (400 MHz, $CDCL_3$-d_6) δ 1.38 (3H, t, J = 7.1 Hz), 3.50 - 3.40 (1H, m), 4.35 (2H, q, J = 7.2 Hz), 4.67 - 4.51 (4H, m), 4.72 (2H, s), 7.22 - 7.08 (2H, m), 7.46 - 7.34 (2H, m), 7.44 (1H, t, C<u>H</u>F_2), 8.35 (1H, s).

MS ^{m}/z: 497 (M +1)

Example 157

Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method A' from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate. Yield: 41 mg (78 %).

1H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 6.8 Hz), 1.60 - 1.68 (2H, m), 1.85 - 1.90 (2H, m), 2.57 - 2.64 (1H, m), 3.17 - 3.24 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 4.53 - 4.58 (2H, m), 4.72 (2H, s), 7.20 - 7.26 (2H, m), 7.35 - 7.45 (2H, m), 7.37 (1H, t, J = 54.1 Hz), 8.47 (1H, s)

MS m/z: 525 (M+1)

Example 158

Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method A' from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-fluorophenyl)methanesulfonamide to give Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate. Yield: 21 mg (40 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 8.45 (1H, s), 7.35 (1H, t, J = 53.5 Hz), 7.38 - 7.43 (1H, m), 7.16 - 7.22 (1H, m), 7.05 - 7.11 (2H, m), 4.69 (2H, s), 4.48 - 4.55 (2H, m), 4.24 (2H, q, J = 7.1 Hz), 3.14 - 3.21 (2H, m), 2.53 - 2.58 (1H, m), 1.78 - 1.84 (2H, m), 1.56 - 1.65 (2H, m), 1.27 (3H, t, J = 7.1 Hz)

MS $^m/_z$: 525 (M+1)

Example 159

Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-fluorophenyl)methanesulfonamide to give Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate. Yield: 19 mg (36 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.2 Hz), 1.58 - 1.67 (2H, m), 1.81 - 1.87 (2H, m), 3.15 - 3.22 (2H, m), 4.26 (2H, q, J = 7.1 Hz), 4.51 - 4.58 (2H, m), 4.66 (2H, s), 7.19 - 7.23 (2H, m), 7.28 - 7.32 (2H, m), 7.37 (1H, t, J = 54.1 Hz), 8.47 (1H, s)
Note! One H is hidden in the DMSO signal
MS $^m/_z$: 525 (M+1)

Example 160

Ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2-chlorophenyl)methanesulfonamide to give Ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate. Yield: 36 mg (67 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.2 Hz), 1.60 - 1.69 (2H, m), 1.86 - 1.92 (2H, m), 3.18 - 3.24 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 4.51 - 4.59 (2H, m), 4.81 (2H, s), 7.26 - 7.53 (5H, m), 8.47 (1H, s). Note! One H is hidden in the DMSO signal
MS $^m/_z$: 541 (M+1)

Example 161

Ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-chlorophenyl)methanesulfonamide to give Ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate. Yield: 42 mg (78 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27 (3H, t, J = 6.8 Hz), 1.57 - 1.65 (2H, m), 1.78 - 1.84 (2H, m), 2.53 - 2.59 (1H, m), 3.14 - 3.21 (2H, m), 4.24 (2H, q, J = 6.9 Hz), 4.49 - 4.56 (2H, m), 4.68 (2H, s), 7.18 - 7.46 (5H, m), 8.46 (1H, s)
MS $^m/_z$: 541 (M+1)

Example 162

Ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-chlorophenyl)methanesulfonamide to give Ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate. Yield: 33 mg (61 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.2 Hz), 1.58 - 1.72 (2H, m), 1.82 - 1.92 (2H, m), 2.56 - 2.68 (1H, m), 3.16 - 3.26 (2H, m), 4.28 (2H, q, J = 7.2 Hz), 4.52 - 4.61 (2H, m), 4.70 (2H, s), 7.28 - 7.35 (2H, m), 7.39 (1H, t, J = 54.1 Hz), 7.44 - 7.51 (2H, m), 8.50 (1H, s), 11.64 (1H, s)

MS $^{m}/_{z}$: 541 (M+1)

Example 163

Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-methylphenyl)methanesulfonamideto give ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate. Yield: 17 mg (32 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.3 Hz), 1.59 - 1.73 (2H, m), 1.79 - 1.89 (2H, m), 2.29 (3H, s), 2.54 - 2.64 (1H, m), 3.16 - 3.26 (2H, m), 4.28 (2H, q, J = 7.4 Hz), 4.53 - 4.61 (2H, m), 4.63 (2H, s), 7.04 - 7.10 (2H, m), 7.16 - 7.22 (1H, m), 7.24 - 7.31 (1H, m), 7.39 (1H, t, J = 53.9 Hz), 8.49 (1H, s), 11.59 (1H, s)

MS $^{m}/_{z}$: 521 (M+1)

Example 164

Ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-methylphenyl)methanesulfonamideto give ethyl 5-cyano-2-(difluoromethyl)-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate. Yield: 19 mg (36 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27 (3H, t, J = 7.2 Hz), 1.57 - 1.65 (2H, m), 1.79 - 1.85 (2H, m), 2.26 (3H, s), 3.14 - 3.21 (2H, m), 4.24 (2H, q, J = 7.3 Hz), 4.50 - 4.56 (2H, m), 4.58 (2H, s), 7.10 - 7.18 (4H, m), 7.36 (1H, t, J = 53.4 Hz), 8.46 (1H, s).Note! One H is hidden in the DMSO signal.

MS $^{m}/_{z}$: 521 (M+1)

Example 165

Ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2,4-dichlorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 27 mg (47 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.0 Hz), 1.59 - 1.68 (2H, m), 1.87 - 1.93 (2H, m), 2.54 - 2.60 (1H, m), 3.18 - 3.24 (2H, m), 4.26 (2H, q, J = 6.8 Hz), 4.52 - 4.58 (2H, m), 4.81 (2H, s), 7.26 - 7.52 (3H, m), 7.69 (1H, s), 8.47 (1H, s)

MS$^m/_z$: 575 (M+1)

Example 166

Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-fluorophenyl)methanesulfonamide to give Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate. Yield: 47 mg (95%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.3 Hz), 3.51 - 3.59 (1H, m), 4.25 (2H, q, J = 7.4 Hz), 4.26 - 4.51 (4H, m), 4.75 (2H, s), 7.12 - 7.22 (3H, m), 7.35 - 7.42 (1H, m), 7.37 (1H, t, J = 53.2 Hz), 8.44 (1H, s)

MS $^m/_z$: 497 (M+1)

Example 167

Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-fluorophenyl)methanesulfonamide to give Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate. Yield: 41 mg (83%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.1 Hz), 3.49 - 3.57 (1H, m), 4.23 (2H, q, J = 7.1 Hz), 4.26 - 4.50 (4H, m), 4.69 (2H, s), 7.12 - 7.19 (2H, m), 7.32 - 7.37 (2H, m), 7.36 (1H, t, J = 54.2 Hz), 8.43 (1H, s)

MS $^m/_z$: 497 (M+1)

Example 168

Ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2-chlorophenyl)methanesulfonamide to give ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate. Yield: 42 mg (82 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.58 - 3.68 (1H, m), 4.27 (2H, q, J = 7.5 Hz), 4.36 - 4.57 (4H, m), 4.90 (2H, s), 7.35 - 7.46 (2H, m), 7.40 (1H, t, J = 54.2 Hz), 7.47 - 7.56 (2H, m), 8.47 (1H, s), 12.03 (1H, s)

MS $^m/_z$: 513 (M+1)

Example 169

Ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-chlorophenyl)methanesulfonamide to give ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate. Yield: 46 mg (90 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.1 Hz), 3.51 - 3.59 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.25 - 4.54 (4H, m), 4.76 (2H, s), 7.26 - 7.30 (1H, m), 7.35 - 7.47 (4H, m), 8.44 (1H, s).

MS $^m/_z$: 513 (M+1)

Example 170

Ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-chlorophenyl)methanesulfonamide to give ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(difluoromethyl)nicotinate. Yield: 45 mg (88 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.0 Hz), 3.50 - 3.57 (1H, m), 4.23 (2H, q, J = 7.0 Hz), 4.27 - 4.50 (4H, m), 4.70 (2H, s), 7.30 - 7.34 (2H, m), 7.36 (1H, t, J = 53.8 Hz), 7.38 - 7.43 (2H, m), 8.43 (1H, s).

MS $^m/_z$: 513 (M+1)

Example 171

Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-methylphenyl)methanesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate. Yield: 36 mg (73 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.6 Hz), 2.22 (3H, s), 3.48 - 3.56 (1H, m), 4.23 (2H, q, J = 7.0 Hz), 4.24 - 4.49 (4H, m), 4.64 (2H, s), 7.06 - 7.10 (2H, m), 7.12 - 7.16 (1H, m), 7.19 - 7.23 (1H, m), 7.36 (1H, t, J = 54.9 Hz), 8.43 (1H, s)

MS $^m/_z$: 493 (M+1)

Example 172

Ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-methylphenyl)methanesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate. Yield: 31 mg (63 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 6.9 Hz), 2.24 (3H, s), 3.47 - 3.55 (1H, m), 4.23 (2H, q, J = 6.9 Hz), 4.26 - 4.49 (4H, m), 4.63 (2H, s), 7.11 - 7.19 (4H, m), 7.36 (1H, t, J = 53.8 Hz), 8.43 (1H, s)

MS $^m/_z$: 493 (M+1)

Example 173

Ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2,4-dichlorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 7 mg (12 %).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.3 Hz), 3.44 - 3.55 (1H, m), 4.23 (2H, q, J = 7.3 Hz), 4.29 - 4.52 (4H, m), 4.67 - 4.83 (2H, m), 7.35 (1H, t, J = 54.3 Hz), 7.38 - 7.50 (2H, m), 7.57 - 7.64 (1H, m), 8.42 (1H, s)

MS $^m/_z$: 547 (M+1)

Example 174

Ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-methylcyclohexyl)methanesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate. Yield: 27 mg (55 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 - 0.95 (3H, m), 1.01 - 1.20 (2H, m), 1.30 (3H, t, J = 7.0 Hz), 1.40 - 1.58 (5H, m), 1.60 - 1.88 (2H, m), 2.04 - 2.15 (1H, m), 3.40 - 3.45 (2H, m), 3.59 - 3.69 (1H, m), 4.26 (2H, q, J = 7.4 Hz), 4.33 - 4.58 (4H, m), 7.38 (1H, t, J = 54.3 Hz), 8.46 (1H, s), 11.93 (1H, s)

MS $^m/_z$: 499 (M+1)

Example 175

Ethyl 5-cyano-6-[3-({[(3-cyanophenyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 3-cyanobenzenesulfonamide to give ethyl 5-cyano-6-[3-({[(3-cyanophenyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 47 mg (64 %).

MS ^{m}/z: 490 (M +1)

Example 176

Ethyl 5-cyano-6-[3-({[(4-cyanophenyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 4-cyanobenzenesulfonamide to give ethyl 5-cyano-6-[3-({[(4-cyanophenyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 42 mg (57 %).

MS ^{m}/z: 490 (M +1)

Example 177

Ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

Prepared according to Method A´ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 4-(trifluoromethoxy)benzenesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[4-

(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate. Yield: 37 mg (45 %).
MS ^{m}/z: 549 (M +1)

Example 178

Ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 2-(trifluoromethoxy)benzenesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-{3-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate. Yield: 44 mg (53 %).
MS ^{m}/z: 549 (M +1)

Example 179

Ethyl 5-cyano-6-[3-({[(2-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2-cyanophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(2-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 52 mg (69%).
MS ^{m}/z: 504 (M +1)

Example 180

Ethyl 5-cyano-2-(difluoromethyl)-6-(3-{[(2-naphthylsulfonyl)amino]carbonyl}azetidin-1-yl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and naphthalene-2-sulfonamide to

give ethyl 5-cyano-2-(difluoromethyl)-6-(3-{[(2-naphthylsulfonyl)amino]carbonyl}azetidin-1-yl)nicotinate. Yield: 48 mg (62 %).
MS ^{m}/z: 515 (M +1)

Example 181

Ethyl 6-(3-{[(butylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A' from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]azetidine-3-carboxylic acid and butane-1-sulfonamide to give ethyl 6-(3-{[(butylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate. Yield: 44 mg (65 %).
MS ^{m}/z: 445 (M +1)

Example 182

Ethyl 5-cyano-6-[4-({[(3-cyanophenyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A' from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 3-cyanobenzenesulfonamide to give ethyl 5-cyano-6-[4-({[(3-cyanophenyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 9 mg (12 %).
MS ^{m}/z: 518 (M +1)

Example 183

Ethyl 5-cyano-6-[4-({[(4-cyanophenyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A' from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 4-cyanobenzenesulfonamide to give ethyl 5-cyano-6-[4-({[(4-cyanophenyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate. Yield: 9 mg (12 %).
MS ^{m}/z: 518 (M +1)

Example 184

Ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 4-(trifluoromethoxy)benzenesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[4-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate. Yield: 17 mg (19%).

MS ^{m}/z: 577 (M +1)

Example 185

Ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 2-(trifluoromethoxy)benzenesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate. Yield: 50 mg (58 %).

MS ^{m}/z: 577 (M +1)

Example 186

Ethyl 5-cyano-6-[4-({[(2-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and 2-(trifluoromethoxy)benzenesulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-{4-[({[2-(trifluoromethoxy)phenyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate. Yield: 14 mg (17 %).

MS ^{m}/z: 532 (M +1)

Example 187

Ethyl 5-cyano-2-(difluoromethyl)-6-(4-{[(2-naphthylsulfonyl)amino]carbonyl}piperidin-1-yl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and naphthalene-2-sulfonamide to give ethyl 5-cyano-2-(difluoromethyl)-6-(4-{[(2-naphthylsulfonyl)amino]carbonyl}piperidin-1-yl)nicotinate. Yield: 31 mg (38 %).

MS ^{m}/z: 543 (M +1)

Example 188

Ethyl 6-(4-{[(butylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

Prepared according to Method A′ from 1-[3-cyano-6-(difluoromethyl)-5-(ethoxycarbonyl)pyridin-2-yl]piperidine-4-carboxylic acid and butane-1-sulfonamide to give ethyl 6-(4-{[(butylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate. Yield: 36 mg (51 %).

MS ^{m}/z: 473 (M +1)

Example 189

Ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}pyrrolidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

(a) {1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}acetic acid

TEA (606 mg, 5.99 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate (341mg, 1.2 mmol) and pyrrolidin-3-ylacetic acid (209 mg, 1.62 mmol) in water/EtOH (4.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 20 minutes. The solvent was evaporated and the residue was taken up in DCM and

washed with 1 % $KHSO_4$.The combined aqueous phase was extracted with DCM and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 5 % CH_3CN to 100 % CH_3CN/(0.2 % HOAc(aq)) gave {1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}acetic acid as a white solid. Yield: 219 mg (49 %).

^{1}H NMR (400MHz, $CDCL_3$) δ 1.35 (3H, t, J = 7.2 Hz), 1.85 - 1.68 (1H, m), 2.38 - 2.23 (1H, m), 2.64 - 2.47 (2H, m), 2.81 - 2.66 (1H, m), 3.57 - 3.40 (1H, m), 3.91 - 3.77 (1H, m), 4.08 - 3.97 (1H, m), 4.21 - 4.10 (1H, m), 4.33 (2H, q, J = 7.3 Hz), 8.31 (1H, s).

MS $^m/_z$: 371 (M+1)

(b) ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}pyrrolidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method B′ from {1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}acetic acid and 1-phenylmethanesulfonamide to give ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}pyrrolidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 88 mg (84 %).

^{1}H NMR (600 MHz, DMSO) d 1.26 (3H, t, *J* = 7.3 Hz), 1.59-1.68 (1H, m), 2.09-2.17 (1H, m), 2.40-2.44 (2H, m), 3.64-3.77 (1H, m), 3.81-3.91 (1H, m), 3.94-4.06 (1H, m), 4.24 (2H, q, *J* = 7.0 Hz), 4.68 (2H, s), 7.24-7.39 (5H, m), 8.45 (1H, s). Note! One H hidden in the DMSO peak and one H hidden in the H_2O peak

MS $^m/_z$: 525 (M+1)

Example 190

Ethyl 5-cyano-6-[3-(2-oxo-2-{[(2-phenylethyl)sulfonyl]amino}ethyl)pyrrolidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method B′ from {1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}acetic acid and 2-phenylethanesulfonamideto give ethyl 5-cyano-6-[3-(2-oxo-2-{[(2-phenylethyl)sulfonyl]amino}ethyl)pyrrolidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 73 mg (68 %).

^{1}H NMR (600 MHz, DMSO) d 1.25 (3H, t, J = 7.0 Hz), 1.58 - 1.66 (1H, m), 2.05 - 2.13 (1H, m), 2.37 - 2.40 (2H, m), 2.92 - 2.98 (2H, m), 3.62 - 3.67 (2H, m), 3.67 - 3.75 (1H, m), 3.80 - 3.99 (2H, m), 4.23 (2H, q, J = 7.3 Hz), 7.15 - 7.31 (5H, m), 8.43 (1H, s). Note! One H hidden in the DMSO peak and one H hidden in the H_2O peak

MS $^m/_z$: 537 (M-1)

Example 191

Ethyl 6-[3-(2-{[(5-chloro-2-thienyl)sulfonyl]amino}-2-oxoethyl)pyrrolidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method B´ from {1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}acetic acid and 5-chlorothiophene-2-sulfonamide to give ethyl 6-[3-(2-{[(5-chloro-2-thienyl)sulfonyl]amino}-2-oxoethyl)pyrrolidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 86 mg (78 %).

^{1}H NMR (500 MHz, DMSO) d 1.29 (3H, t, J = 6.9 Hz), 1.60 - 1.69 (1H, m), 2.06 - 2.14 (1H, m), 2.44 - 2.48 (1H, m), 2.55 - 2.60 (1H, m), 3.33 - 3.39 (1H, m), 3.68 - 3.76 (1H, m), 3.84 - 3.96 (2H, m), 4.28 (2H, q, J = 7.2 Hz), 7.22 (1H, d, J = 4.2 Hz), 7.63 (1H, d, J = 4.2 Hz), 8.41 (1H, s).

MS $^m/_z$: 549 (M-1)

Example 192

Ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

(a) 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid

TEA (0.908 g, 8.97 mmol) was added to a suspension of ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate (1.0 g, 3.59 mmol) and azetidine-3-carboxylic acid (0.399 g, 3.95 mmol) in EtOH (10 mL) and the mixture was heated in a single-node microwave oven for 20 mionutes. The solvent was evaporated and the residue was partioned between iPrOAc (10 mL)/water and Na2CO3. The aqueous phase was separated and made acidic by addition of concentrated HCl. The acidic water phase was extracted with iPrOAc (2 x 10 mL). The

combined extracts was dried (MgSO4) and evaporated to give 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid as a brown solid which was used without further purification. Yield 1.04 g (84 %).
1H-NMR (500 MHz, DMSO-d_6) δ 1.27 (3H, t, J= 7.1 Hz), 3.55-3.62 (1H, m), 4.28 (2H, q, J= 7.1 Hz), 4.38-4.58 (4H, m), 8.46 (1H, s).

(b) Ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method D´ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate.
MS ^{m}/z: 515 (M +1)

Example 193

Ethyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method D´ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate.
MS ^{m}/z: 515 (M +1)

Example 194

Ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method D´ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

MS ^{m}/z: 515 (M +1)

Example 195

Ethyl 5-cyano-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-methylphenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate.
MS ^{m}/z: 511 (M +1)

Example 196

Ethyl 5-cyano-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-methylphenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate.
MS ^{m}/z: 511 (M +1)

Example 197

Ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-chlorophenyl)methanesulfonamideto give ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate.
MS ^{m}/z: 531 (M +1)

Example 198

Ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2-chlorophenyl)methanesulfonamideto give ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. MS ^{m}/z: 531 (M +1)

Example 199

Ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-chlorophenyl)methanesulfonamideto give ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. MS ^{m}/z: 531 (M +1)

Example 200

Ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2,4-dichlorophenyl)methanesulfonamide to give ethyl Ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(trifluoromethyl)nicotinate. MS ^{m}/z: 565 (M +1)

Example 201

Ethyl 6-(3-{[(5-chloro-2-thienyl)sulfonyl]carbamoyl}azetidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method D′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 5-chlorothiophene-2-sulfonamide to give ethyl 6-(3-{[(5-chloro-2-thienyl)sulfonyl]carbamoyl}azetidin-1-yl)-5-cyano-2-(trifluoromethyl)nicotinate.

MS ^{m}/z: 523 (M +1)

Example 202

Ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

(a) 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid

TEA (0.908 g, 8.97 mmol) was added to a suspension of ethyl 6-chloro-5-cyano-2-(trifluoromethyl)nicotinate (1.0 g, 3.59 mmol) and piperidine-4-carboxylic acid (0.510 g, 3.95 mmol) in EtOH (10 mL) and the mixture was heated in a single-node microwave oven for 15 mionutes. The solvent was evaporated and the residue was partioned between iPrOAc (10 mL)/water and 20 % Na2CO3 (1 mL). The aqueous phase was separated, 1 mL EtOH was added and the waterphase was made acidic by addition of concentrated HCl. The acidic water phase was extracted with iPrOAc (2 x 10 mL). The organic phase was dried (MgSO4), filtered and concentrated to give 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid as a brown solid which was used without further purification. Yield: 1.06 g (79 %).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.1 Hz), 1.61-1.71 (2H, m), 1.95-2.02 (2H, m), 2.60-2.68 (1H, m), 3.31-3.38 (2H, m), 4.28 (2H, q, J= 7.1 Hz), 4.41-4.48 (2H, m), 8.51 (1H, s).

(b) Ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(4-

fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 4.3 mg (4 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7 Hz), 1.78-1.94 (4H, m), 2.49-2.55 (1H, m), 3.23 (2H, t, J = 12.5 Hz), 4.35 (2H, q, J = 7 Hz), 4.60 (2H, s), 4.67 (2H, br d, J = 12.5 Hz), 7.06 (2H, t, J = 8.5 Hz), 7.31 (2H, dd, J = 5, 8.5 Hz), 8.34 (1H, s), 9.50 (1H, s).

MS $^m/_z$: 543 (M+1)

Example 203

Ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method C´ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 5.7 mg (5 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 1.81-1.97 (4H, m), 2.53-2.61 (1H, m), 3.28 (2H, t, J = 12.5 Hz), 4.39 (2H, q, J = 7.5 Hz), 4.67 (2H, s), 4.71 (2H, br d, J = 12.5 Hz), 7.12-7.15 (3H, m), 7.36-7.41 (1H, m), 8.38 (1H, s), 9.68 (1H, s).

MS $^m/_z$: 543 (M+1)

Example 204

Ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method C´ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 5.1 mg (5 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 6.5 Hz), 1.80-1.99 (4H, m), 2.53-2.61 (1H, m), 3.27 (2H, t, J = 13 Hz), 4.34 (2H, q, J = 6.5 Hz), 4.67 (2H, br d, J = 13 Hz), 4.69 (2H, s), 7.11 (1H, t, J = 9 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.34-7.39 (2H, m), 8.33 (1H, s), 9.63 (1H, s).
MS $^m/_z$: 543 (M+1)

Example 205

Ethyl 5-cyano-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-methylphenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 3.4 mg (3 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.5 Hz), 1.75-1.93 (4H, m), 2.34 (3H, s), 2.44-2.52 (1H, m), 3.23 (2H, t, J = 12.5 Hz), 4.35 (2H, q, J = 7.5 Hz), 4.58 (2H, s), 4.66 (2H, br d, J = 12.5 Hz), 7.15-7.21 (4H, m), 8.33 (1H, s), 8.88 (1H, s).
MS $^m/_z$: 539 (M+1)

Example 206

Ethyl 5-cyano-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-methylphenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 2.8 mg (3 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, J = 7.5 Hz), 1.71-1.88 (4H, m), 2.28 (3H, s), 2.39-2.47 (1H, m), 3.18 (2H, t, J = 13 Hz), 4.30 (2H, q, J = 7.5 Hz), 4.54 (2H, s), 4.61 (2H, br d, J = 13 Hz), 7.05-7.23 (4H, m), 8.29 (1H, s), 8.72 (1H, s).
MS $^m/_z$: 539 (M+1)

Example 207

Ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-chlorophenyl)methanesulfonamide to give ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 6.6 mg (6 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 7.5 Hz), 1.63-1.70 (2H, m), 1.74-1.79 (2H, m), 2.39-2.41 (1H, m), 3.09 (2H, t, J = 12.5 Hz), 4.18 (2H, q, J = 7.5 Hz), 4.42 (2H, s), 4.52 (2H, br d, J = 12.5 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 8.18 (1H, s), 11.32 (1H, s).

MS $^m/_z$: 559 (M+1)

Example 208

Ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2-chlorophenyl)methanesulfonamide to give ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 7.8 mg (7 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 7 Hz), 1.81-1.90 (2H, m), 1.96-2.00 (2H, m), 2.56-2.64 (1H, m), 3.26 (2H, t, J = 12 Hz), 4.34 (2H, q, J = 7 Hz), 4.68 (2H, br d, J = 12 Hz), 4.84 (2H, s), 7.27-7.34 (2H, m), 7.42 (2H, t, J = 7 Hz), 8.34 (1H, s), 10.03 (1H, s).

MS $^m/_z$: 559 (M+1)

Example 209

Ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-chlorophenyl)methanesulfonamide to give ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 7.3 mg (6 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 1.81-1.90 (2H, m), 1.91-1.97 (2H, m), 2.54-2.62 (1H, m), 3.28 (2H, t, J = 12.5 Hz), 4.39 (2H, q, J = 7.5 Hz), 4.64 (2H, s), 4.72 (2H, br d, J = 12.5 Hz), 7.25 (1H, d, J = 7.5 Hz), 7.34-7.42 (3H, m), 8.38 (1H, s), 10.02 (1H, s).

MS $^m/_z$: 559 (M+1)

Example 210

Ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2,4-dichlorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(trifluoromethyl)nicotinate. Yield: 5.5 mg (5 %).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 7.5 Hz), 1.83-1.90 (2H, m), 1.97-2.01 (2H, m), 2.56-2.64 (1H, m), 3.29 (2H, t, J = 12.5 Hz), 4.34 (2H, q, J = 7.5 Hz), 4.68 (2H, br d, J = 12.5 Hz), 4.80 (2H, s), 7.28 (1H, dd, J = 2, 8.5 Hz), 7.37 (1H, d, J = 8.5 Hz), 7.45 (1H, d, J = 2 Hz), 8.33 (1H, s), 10.04 (1H, s).

MS $^m/_z$: 593 (M+1).

Example 211

Ethyl 6-[4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate

Prepared according to Method C′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 5-chlorothiophene-2-sulfonamideto give ethyl 6-[4-({[(5-chloro-2-thienyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(trifluoromethyl)nicotinate. Yield: 19.1 mg (17 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7 Hz), 1.72-1.84 (2H, m), 1.91-1.97 (2H, m), 2.55-2.65 (1H, m), 3.27 (2H, t, J = 12.5 Hz), 4.33 (2H, q, J = 7.5 Hz), 4.61 (2H, br d, J = 12.5 Hz), 6.91 (1H, d, J = 4 Hz), 7.62 (1H, d, J = 4 Hz), 8.30 (1H, s), 10.99 (1H, s).
MS $^m/_z$: 551 (M+1)

Example 212

Ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

(a) 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid

TEA (653 mg, 6.46 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(fluoromethyl)nicotinate (400mg, 1.61 mmol) and azetidine-3-carboxylic acid (179 mg, 1.78 mmol) in water/ EtOH (4.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 20 minutes. The solvent was evaporated and the residue was taken up in DCM and washed with 1 % KHSO4 . The aqueous phase was extracted with DCM and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 5 % CH3CN to 100 % CH3CN/(0.2 % HOAc(aq)) gave 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid as a white solid. Yield 302 mg (60 %).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, J= 7.3 Hz), 3.59-3.69 (1H, m), 4.31 (2H, q, J= 7.3 Hz), 4.60-4.70 (4H, m), 5.69 (2H, d, J= 47.3 Hz), 8.30 (1H, br s).

(b) Ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 21 mg (44 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.55 - 3.66 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.34 - 4.44 (2H, m), 4.43 - 4.56 (2H, m), 4.80 (2H, s), 5.68 (2H, d, J = 47.1 Hz), 7.18 - 7.32 (2H, m), 7.37 - 7.52 (2H, m), 8.39 (1H, s), 11.80 - 12.19 (1H, m)
MS ^{m}/z: 479 (M+1).

Example 213

Ethyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 25 mg (53 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 3.54 - 3.64 (1H, m), 4.24 (2H, q, J = 7.1 Hz), 4.28 - 4.36 (2H, m), 4.39 - 4.53 (2H, m), 4.79 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.13 - 7.27 (3H, m), 7.37 - 7.47 (1H, m), 8.38 (1H, s), 11.55 - 12.36 (1H, m)
MS ^{m}/z: 479 (M+1).

Example 214

Ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 27 mg (56 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.55 - 3.77 (1H, m), 4.24 (2H, q, J = 7.1 Hz), 4.29 - 4.37 (2H, m), 4.41 - 4.51 (2H, m), 4.73 (2H, s), 5.66 (2H, d, J = 47.1 Hz), 7.15 - 7.23 (2H, m), 7.34 - 7.42 (2H, m), 8.37 (1H, s).
MS ^{m}/z: 479 (M+1).

Example 215

Ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2-chlorophenyl)methanesulfonamide to give ethyl 6-[3-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate.
Yield: 13 mg (27 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.59 - 3.69 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.36 - 4.56 (4H, m), 4.90 (2H, s), 5.67 (2H, d, J = 47.3 Hz), 7.34 - 7.56 (4H, m), 8.38 (1H, s), 11.73 - 12.28 (1H, m)
MS ^{m}/z: 495 (M+1).

Example 216

Ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-chlorophenyl)methanesulfonamide to give ethyl 6-[3-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate.
Yield: 28 mg (58 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.51 - 3.65 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.27 - 4.37 (2H, m), 4.40 - 4.53 (2H, m), 4.79 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.27 - 7.50 (4H, m), 8.36 - 8.40 (1H, m), 11.71 - 12.13 (1H, m)
MS ^{m}/z: 495 (M+1).

Example 217

Ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-chlorophenyl)methanesulfonamide to give ethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate. Yield: 33 mg (68 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.45 - 3.58 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.29 - 4.38 (2H, m), 4.38 - 4.50 (2H, m), 4.60 (2H, s), 5.66 (2H, d, J = 47.1 Hz), 7.29 - 7.41 (4H, m), 8.36 (1H, s).

MS ^{m}/z: 495 (M+1).

Example 218

Ethyl 5-cyano-2-(fluoromethyl)-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(3-methylphenyl)methanesulfonamide to give ethyl 5-cyano-2-(fluoromethyl)-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate. Yield: 41 mg (86 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 2.27 (3H, s), 3.51 - 3.60 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.29 - 4.37 (2H, m), 4.39 - 4.51 (2H, m), 4.69 (2H, s), 5.67 (2H, d, J = 50.0 Hz), 7.07 - 7.32 (4H, m), 8.38 (1H, s), 11.59 - 12.03 (1H, m)

MS ^{m}/z: 475 (M+1).

Example 219

Ethyl 5-cyano-2-(fluoromethyl)-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-methylphenyl)methanesulfonamide to give ethyl 5-cyano-2-(fluoromethyl)-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate. Yield: 12 mg (25 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 2.28 (3H, s), 3.53 - 3.60 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.29 - 4.36 (2H, m), 4.39 - 4.50 (2H, m), 4.67 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.15 - 7.23 (4H, m), 8.37 - 8.40 (1H, m), 11.48 - 12.04 (1H, m)
MS ^{m}/z: 475 (M+1).

Example 220

Ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(2,4-dichlorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 27 mg (51%).
^{1}H NMR 400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.56 - 3.65 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.35 - 4.58 (4H, m), 4.86 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.41 - 7.70 (3H, m), 8.36 - 8.39 (1H, m).
MS ^{m}/z: 529 (M+1).

Example 221

Ethyl 5-cyano-2-(fluoromethyl)-6-{3-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid and 1-(4-methylcyclohexyl)methanesulfonamide to give ethyl 5-cyano-6-[3-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 28 mg (57 %).
^{1}H NMR (400MHz, DMSO-d_6) δ 0.75 - 0.92 (4H, m), 0.95 - 1.17 (3H, m), 1.25 (3H, t, J = 7.1 Hz), 1.35 - 1.54 (4H, m), 1.55 - 1.64 (1H, m), 1.74 - 1.84 (1H, m), 2.00 - 2.10 (1H, m), 3.22 - 3.28 (1H, m), 3.51 - 3.63 (1H, m), 4.20 (2H, q, J = 7.1 Hz), 4.29 - 4.39 (2H, m), 4.40 - 4.51 (2H, m), 5.61 (2H, d, J = 47.3 Hz), 8.32 (1H, s).
MS ^{m}/z: 481 (M+1).

Example 222

Ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

(a) 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid

TEA (653 mg, 6.46 mmol) was added to a solution of ethyl 6-chloro-5-cyano-2-(fluoromethyl)nicotinate (400mg, 1.61 mmol) and piperidine-4-carboxylic acid (229 mg, 1.78 mmol) in water/ EtOH (4.5 mL). The mixture was heated in a single-node microwave oven at 120 °C for 20 minutes. The solvent was evaporated and the residue was taken up in DCM and washed with 1 % KHSO4 . The aqueous phase was extracted with DCM and the combined organic phase was filtered through a phase separator and concentrated. Purification by HPLC (Kromasil C8, Eluent : A gradient of 5 % CH3CN to 100 % CH3CN/(0.2 % HOAc(aq)) gave 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]azetidine-3-carboxylic acid as a white solid. Yield 76 mg (14 %).

^{1}H NMR (400 MHz, $CDCL_3$) δ 1.36 (3H, t, J = 7.2 Hz), 1.82-1.94 (2H, m), 2.05-2.14 (2H, m), 2.66-2.76 (1H, m), 3.32-3.42 (2H, m), 4.31 (2H, t, J= 7.2 Hz), 4.61-4.69 (2H, m), 5.70 (2H, d, J = 47.3Hz), 8.36 (1H, br s).

(b) Ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E´ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 13 mg (25 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 1.56 - 1.75 (2H, m), 1.82 - 1.93 (2H, m), 2.56 - 2.64 (1H, m), 3.14 - 3.26 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.55 - 4.64 (2H, m), 4.68 (2H, s), 5.68 (2H, d, J = 47.1 Hz), 7.18 - 7.30 (2H, m), 7.32 - 7.48 (2H, m), 8.39 (1H, s).

MS ^{m}/z: 507 (M+1).

Example 223

Ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 16 mg (31 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.56 - 1.71 (2H, m), 1.79 - 1.89 (2H, m), 2.55 - 2.61 (1H, m), 3.15 - 3.26 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.53 - 4.64 (2H, m), 4.70 (2H, s), 5.69 (2H, d, J = 47.1 Hz), 7.07 - 7.17 (2H, m), 7.20 - 7.28 (1H, m), 7.39 - 7.49 (1H, m), 8.39 - 8.42 (1H, m), 11.47 - 12.06 (1H, m)

MS ^{m}/z: 507 (M+1).

Example 224

Ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-fluorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate. Yield: 23 mg (45 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 1.56 - 1.70 (2H, m), 1.78 - 1.89 (2H, m), 2.52 - 2.56 (1H, m), 3.14 - 3.24 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.51 - 4.63 (4H, m), 5.68 (2H, d, J = 47.1 Hz), 7.16 - 7.24 (2H, m), 7.27 - 7.34 (2H, m), 8.39 (1H, s).

MS ^{m}/z: 507 (M+1).

Example 225

Ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2-chlorophenyl)methanesulfonamide to give ethyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate. Yield: 24 mg (45 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 1.56 - 1.74 (2H, m), 1.84 - 1.95 (2H, m), 2.56 - 2.66 (1H, m), 3.16 - 3.27 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.54 - 4.65 (2H, m), 4.80 (2H, s), 5.68 (2H, d, J = 47.3 Hz), 7.35 - 7.46 (3H, m), 7.48 - 7.55 (1H, m), 8.39 (1H, s).
MS ^{m}/z: 523 (M+1).

Example 226

Ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-chlorophenyl)methanesulfonamide to give ethyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate. Yield: 24 mg (46 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.57 - 1.70 (2H, m), 1.76 - 1.88 (2H, m), 2.53 - 2.61 (1H, m), 3.15 - 3.27 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.55 - 4.63 (2H, m), 4.68 (2H, s), 5.68 (2H, d, J = 47.3 Hz), 7.18 - 7.52 (4H, m), 8.40 (1H, s).
MS ^{m}/z: 523 (M+1).

Example 227

Ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-chlorophenyl)methanesulfonamide to give ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-(fluoromethyl)nicotinate.
Yield: 24 mg (46 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.71 (2H, m), 1.80 - 1.90 (2H, m), 2.54 - 2.60 (1H, m), 3.13 - 3.26 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.55 - 4.63 (2H, m), 4.66 (2H, s), 5.68 (2H, d, J = 47.1 Hz), 7.30 (2H, d, J = 8.5 Hz), 7.46 (2H, d, J = 8.5 Hz), 8.38 - 8.41 (1H, m).
MS ^{m}/z: 523 (M+1).

Example 228

Ethyl 5-cyano-2-(fluoromethyl)-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(3-methylphenyl)methanesulfonamide to give ethyl 5-cyano-2-(fluoromethyl)-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate.
Yield: 6 mg (12 %).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.58 - 1.71 (2H, m), 1.79 - 1.88 (2H, m), 2.28 (3H, s), 2.52 - 2.58 (1H, m), 3.17 - 3.23 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.48 - 4.68 (4H, m), 5.68 (2H, d, J = 47.1 Hz), 7.00 - 7.32 (4H, m), 8.40 (1H, s), 11.27 - 11.80 (1H, m).
MS ^{m}/z: 503 (M+1).

Example 229

Ethyl 5-cyano-2-(fluoromethyl)-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-

methylphenyl)methanesulfonamide to give ethyl 5-cyano-2-(fluoromethyl)-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate.

Yield: 20 mg (40 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.57 - 1.72 (2H, m), 1.80 - 1.92 (2H, m), 2.30 (3H, s), 2.54 - 2.64 (1H, m), 3.11 - 3.25 (2H, m), 4.26 (2H, q, J = 7.2 Hz), 4.52 - 4.68 (4H, m), 5.69 (2H, d, J = 47.3 Hz), 7.11 - 7.28 (4H, m), 8.41 (1H, s), 11.33 - 11.86 (1H, m).

MS ^{m}/z: 503 (M+1).

Example 230

Ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(2,4-dichlorophenyl)methanesulfonamide to give ethyl 5-cyano-6-[4-({[(2,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-(fluoromethyl)nicotinate.

Yield: 21 mg (38 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.72 (2H, m), 1.83 - 1.94 (2H, m), 2.54 - 2.59 (1H, m), 3.15 - 3.27 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.53 - 4.63 (2H, m), 4.73 (2H, s), 5.68 (2H, d, J = 47.3 Hz), 7.39 - 7.53 (2H, m), 7.62 - 7.70 (1H, m), 8.35 - 8.43 (1H, m).

MS ^{m}/z: 557 (M+1).

Example 231

Ethyl 5-cyano-2-(fluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

Prepared according to Method E′ from 1-[3-cyano-5-(ethoxycarbonyl)-6-(fluoromethyl)pyridin-2-yl]piperidine-4-carboxylic acid and 1-(4-methylcyclohexyl)methanesulfonamide to give ethyl 5-cyano-2-(fluoromethyl)-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate.

Yield: 18 mg (36 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 - 0.90 (4H, m), 0.96 - 1.20 (3H, m), 1.29 (3H, t, J = 7.2 Hz), 1.38 - 1.69 (7H, m), 1.77 - 1.97 (3H, m), 1.99 - 2.09 (1H, m), 2.59 - 2.71 (2H, m), 3.16 - 3.29 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.51 - 4.66 (2H, m), 5.67 (2H, d, J = 47.3 Hz), 8.39 (1H, s).

MS ^{m}/z: 509 (M+1).

Example 232

Ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

(a) tert-butyl 3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidine-1-carboxylate

DIPEA (0.3 mL, 1.72 mmol) was added to a mixture of [1-(tert-butoxycarbonyl)azetidin-3-yl]acetic acid (193mg, 0.90 mmol) and TBTU (326mg, 1.02 mmol) in dry DCM (4mL). The reaction mixture was stirred at rt for 1h and 1-phenylmethanesulfonamide (169mg, 0.99 mmol) was added and the stirring was continued at r.t for 19h. $NaHCO_3$(aq) was added and the mixture was extracted with EtOAc (3 times). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated to give tert-butyl 3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidine-1-carboxylate which was used in the next step without further purification.

Yield: 383mg (116%).

MS ^{m}/z: 367 (M-1).

(b) 2-azetidin-3-yl-*N*-(benzylsulfonyl)acetamide

The crude tert-butyl 3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidine-1-carboxylate from the previous step (383mg, 0.90 mmol) was dissolved in DCM (5mL) and TFA(4mL) was added. The reaction mixture was stirred at r.t for 1.5 hours. The solvent was evaporated to give 2-azetidin-3-yl-N-(benzylsulfonyl)acetamide which was used in the next step without further purification.Yield: 240 mg (100%)

MS ^{m}/z: 269 (M+1), 267 (M-1).

(c) Ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate

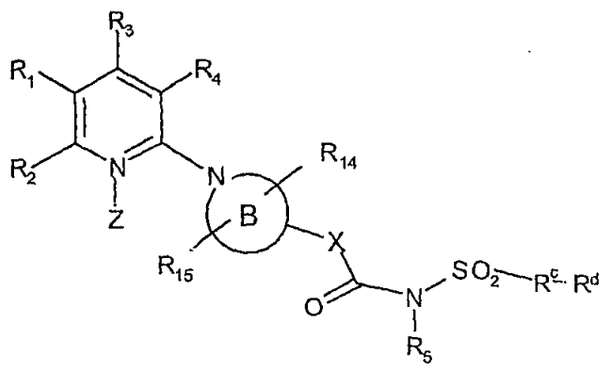
DIPEA (1 mL) was added to a solution of the crude 2-azetidin-3-yl-N-(benzylsulfonyl)acetamide from the previous step and ethyl 6-chloro-5-cyano-2-(difluoromethyl)nicotinate (180mg, 0.69 mmol) in EtOH (9mL). The reaction mixture was heated to 120°C for 5min using microwave single node heating. $NaHCO_3$(aq) was added and the mixture was extracted with DCM (3 times). The combined organic layer was run through a phase separator and evaporated. The crude product was purified by HPLC (Kromasil C8 10µm, 21.5x250mm using a gradient of CH_3CN /0.1 M NH_4OAc 20 % to 50 %, flow 25 mL/min) to give ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-(difluoromethyl)nicotinate. Yield: 156mg (46% over 3steps).

^{1}H NMR (500MHz, DMSO-d_6): δ 1.31 (3H, t, J=7.1Hz), 2.71 (2H, d, J=7.6Hz), 3.04-3.11(1H, m), 4.08 (2H, apparent br s), 4.28 (2H, q, J=7.1Hz), 4.52 (2H, apparent br s), 4.70 (2H, s), 7.29-7.32 (2H, m), 7.37-7.44 (3H, m), 7.40 (1H, t, J=53Hz, -CHF2), 8.44 (1H, s), 11.68 (1H, s).

MS ^{m}/z: 493 (M+1), 491(M-1)

CLAIMS

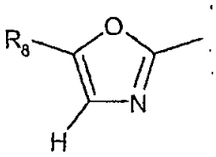
1. A compound of formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 represents $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ or a group gII



(gII);

R_2 represents H, CN, halogen (F, Cl, Br, I), NO_2, (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_1-C_{12})alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkylthioC(O), (C_1-C_{12})alkylC(S), (C_1-C_{12})alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_{12})alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_{12})alkylC(O), (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(2)}$

and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Further, $R_1 + R_2$ together (with two carbon atoms of the pyridine ring) may form a 5-membered or 6-membered cyclic lactone;

R_3 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_1-C_{12})alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkylthioC(O), (C_1-C_{12})alkylC(S), (C_1-C_{12})alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_{12})alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_{12})alkylC(O), (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, COOH, (C_1-C_6)alkoxycarbonyl, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_4 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkylcycloalkyl, (C_1-C_{12})alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or (C_1-C_6)alkoxycarbonyl; further R_4 represents (C_1-C_{12})alkylthioC(O), (C_1-C_{12})alkylC(S), (C_1-C_{12})alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_{12})alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_{12})alkylC(O), (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-

C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(4)}R^{b(4)}$ in which $R^{a(4)}$ and $R^{b(4)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(4)}$ and $R^{b(4)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Z represents O or is absent;

R_5 represents H or (C_1-C_{12})alkyl;

R_6 represents (C_1-C_{12})alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 2 carbon atoms away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_{12})alkyl, aryl or heterocyclyl;

R_7 represents (C_1-C_{12})alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_7 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, aryl or heterocyclyl;

R_8 represents H, (C_1-C_{12})alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_8 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and

$COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_{12})alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl, a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O), (C_1-C_{12})alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_{12})alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{15} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_{12})alkyl, (C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_{12})alkylsulfinyl, (C_1-C_{12})alkylsulfonyl, (C_1-C_{12})alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_{12})alkylthio, aryl(C_1-C_{12})alkylsulfinyl, aryl(C_1-C_{12})alkylsulfonyl, heterocyclyl(C_1-C_{12})alkylthio, heterocyclyl(C_1-C_{12})alkylsulfinyl, heterocyclyl(C_1-C_{12})alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylthio, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(15)}R^{b(15)}$ in which $R^{a(15)}$ and $R^{b(15)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O)), (C_1-C_{12})alkoxyC(O) or $R^{a(15)}$ and $R^{b(15)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{16} represents (C_1-C_{12})alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{16} represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_{12})alkyl,(C_1-C_{12})alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R_{17} represents $(C_1\text{-}C_{12})$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{17} represents $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_{12})$alkyl,$(C_1\text{-}C_{12})$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, aryl or heterocyclyl;

R_{18} represents $(C_1\text{-}C_{12})$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{18} represents $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_{12})$alkyl,$(C_1\text{-}C_{12})$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, aryl or heterocyclyl;

R^c represents an unsubstituted or monosubstituted or polysubstituted $(C_1\text{-}C_4)$alkylene group, $(C_1\text{-}C_4)$oxoalkylene group, $(C_1\text{-}C_4)$alkyleneoxy or oxy-$(C_1\text{-}C_4)$alkylene group, wherein any substituents each individually and independently are selected from $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxyl, oxy-$(C_1\text{-}C_4)$alkyl, $(C_2\text{-}C_4)$alkenyl, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, carboxyl, carboxy-$(C_1\text{-}C_4)$alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, $(C_1\text{-}C_4)$alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; Further R^c represents imino (-NH-), N-substituted imino (-NR_{19}-), $(C_1\text{-}C_4)$alkyleneimino or N-substituted $(C_1\text{-}C_4)$alkyleneimino (-$N(R_{19})$-$((C_1\text{-}C_4)$alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above;

R_{19} represents H or $(C_1\text{-}C_4)$alkyl;

R^d represents $(C_3\text{-}C_8)$cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, $(C_1\text{-}C_{12})$alkyl, $(C_1\text{-}C_{12})$alkoxyC(O), $(C_1\text{-}C_{12})$alkoxy, halogen substituted $(C_1\text{-}C_{12})$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, heterocyclyl, $(C_1\text{-}C_{12})$alkylsulfinyl, $(C_1\text{-}C_{12})$alkylsulfonyl, $(C_1\text{-}C_{12})$alkylthio, $(C_3\text{-}C_6)$cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl$(C_1\text{-}C_{12})$alkylthio, aryl$(C_1\text{-}C_{12})$alkylsulfinyl, aryl$(C_1\text{-}C_{12})$alkylsulfonyl, heterocyclyl$(C_1\text{-}C_{12})$alkylthio, heterocyclyl$(C_1\text{-}C_{12})$alkylsulfinyl, heterocyclyl$(C_1\text{-}C_{12})$alkylsulfonyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_{12})$alkylthio, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}$

C_{12})alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_{12})alkylsulfonyl or a group of formula $NR^{a(Rd)}R^{b(Rd)}$ in which $R^{a(Rd)}$ and $R^{b(Rd)}$ independently represent H, (C_1-C_{12})alkyl, (C_1-C_{12})alkylC(O) or $R^{a(Rd)}$ and $R^{b(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

X represents a single bond, imino (-NH-), methylene (-CH_2-), iminomethylene (-CH_2-NH-) wherein the carbon is connected to the B-ring/ringsystem, methyleneimino (-NH-CH_2-) wherein the nitrogen is connected to the B-ring/ringsystem and any carbon and/or nitrogen in these groups may optionally be substitued with (C_1-C_6) alkyl; further X may represent a group (-CH_2-)n wherein n= 2-6, which optionally is unsaturated and/or substituted by one or more substituent chosen among halogen, hydroxyl and (C_1-C_6)alkyl; and

B is a monocyclic or bicyclic, 4 to 11-membered heterocyclic ring/ring system comprising one or more nitrogen and optionally one or more atoms selected from oxygen or sulphur, which nitrogen is connected to the pyridine-ring (according to formula I) and further the B-ring/ring system is connected to X in another of its positions. The substituents R_{14} and R_{15} are connected to the B ring/ring system in such a way that no quarternary ammonium compounds are formed (by these connections).

2. A compound according to claim 1 wherein

R_2 represents H, CN, NO_2, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_1-C_6)alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_2 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, (C_1-C_6)alkyl, (C_1-

C_6)alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

Further, $R_1 + R_2$ together (with two carbons from the pyridine ring) may form a 5-membered or 6-membered cyclic lactone;

R_3 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_3 represents (C_1-C_6)alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_3 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents H, CN, NO_2, halogen (F, Cl, Br, I), (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, COOH, (C_1-C_6)alkoxycarbonyl, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_4 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or (C_1-C_3)alkoxycarbonyl; further R_4 represents (C_1-C_6)alkylthioC(O), (C_1-C_6)alkylC(S), (C_1-C_6)alkoxyC(O), (C_3-C_6)cycloalkoxy, aryl, arylC(O), aryl(C_1-C_6)alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl(C_1-C_6)alkylC(O), (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or

a group of formula $NR^{a(4)}R^{b(4)}$ in which $R^{a(4)}$ and $R^{b(4)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(4)}$ and $R^{b(4)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_5 represents H or (C_1-C_6)alkyl;

R_6 represents (C_1-C_6)alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 1 carbon atom away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_6)alkyl, aryl or heterocyclyl;

R_7 represents (C_1-C_6)alkyl optionally interrupted by oxygen, and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_7 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, aryl or heterocyclyl;

R_8 represents H, (C_1-C_6)alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_8 represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-

C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl or a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{15} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl,(C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl, (C_3-C_6)cycloalkyl(C_1-C_6)lkylsulfonyl or a group of formula $NR^{a(15)}R^{b(15)}$ in which $R^{a(15)}$ and $R^{b(15)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(15)}$ and $R^{b(15)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{16} represents (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{16} represents (C_3-C_6)cycloalkyl, hydroxy(C_2-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, or heterocyclyl;

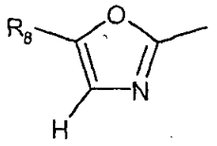
R_{17} represents (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_{17} represents (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl or heterocyclyl;

R_{18} represents $(C_1\text{-}C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms: further R_{18} represents $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkoxy, aryl or heterocyclyl; and

R^d represents $(C_3\text{-}C_8)$cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, OH, CN, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxyC(O), $(C_1\text{-}C_6)$alkoxy, halogen substituted $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, heterocyclyl, $(C_1\text{-}C_6)$alkylsulfinyl, $(C_1\text{-}C_6)$alkylsulfonyl, $(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl$(C_1\text{-}C_6)$alkylthio, aryl$(C_1\text{-}C_6)$alkylsulfinyl, aryl$(C_1\text{-}C_6)$alkylsulfonyl, heterocyclyl$(C_1\text{-}C_6)$alkylthio, heterocyclyl$(C_1\text{-}C_6)$alkylsulfinyl, heterocyclyl$(C_1\text{-}C_6)$alkylsulfonyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkylthio, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkylsulfinyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkylsulfonyl or a group of formula $NR^{a(Rd)}R^{b(Rd)}$ in which $R^{a(Rd)}$ and $R^{b(Rd)}$ independently represent H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylC(O) or $R^{a(Rd)}$ and $R^{b(Rd)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine.

3. A compound according to claim 2 wherein;

R_1 represents $R_6OC(O)$, $R_{16}SC(O)$, or a group gII,



(gII);

R_2 represents H, CN, NO_2, $(C_1\text{-}C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents $(C_1\text{-}C_6)$alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_2 represents $(C_3\text{-}C_6)$cycloalkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylC(O), $(C_1\text{-}C_6)$alkylthioC(O), $(C_1\text{-}C_6)$alkylC(S), $(C_1\text{-}C_6)$alkoxyC(O), $(C_3\text{-}C_6)$cycloalkoxy, aryl, arylC(O), aryl$(C_1\text{-}C_6)$alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl$(C_1\text{-}C_6)$alkylC(O) or a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_3 represents H, CN, NO_2, halogen (F, Cl, Br, I), $(C_1$-$C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_3 represents $(C_1$-$C_6)$alkoxy optionally substituted by one or more halogen (F, Cl, Br, I) atoms; further R_3 represents $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylC(O), $(C_1$-$C_6)$alkylthioC(O), $(C_1$-$C_6)$alkylC(S), $(C_1$-$C_6)$alkoxyC(O), $(C_3$-$C_6)$cycloalkoxy, aryl, arylC(O), aryl$(C_1$-$C_6)$alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl$(C_1$-$C_6)$alkylC(O), $(C_1$-$C_6)$alkylsulfinyl, or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents H, CN, NO_2, halogen (F, Cl, Br, I), $(C_1$-$C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by OH, COOH, aryl, cycloalkyl, heterocyclyl or one or more halogen atoms; further R_4 represents $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylC(O), $(C_1$-$C_6)$alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or methoxycarbonyl; further R_4 represents $(C_1$-$C_6)$alkylthioC(O), $(C_1$-$C_6)$alkylC(S), $(C_1$-$C_6)$alkoxyC(O), $(C_3$-$C_6)$cycloalkoxy, aryl, arylC(O), aryl$(C_1$-$C_6)$alkylC(O), heterocyclyl, heterocyclylC(O), heterocyclyl$(C_1$-$C_6)$alkylC(O) or a group of formula $NR^{a(4)}R^{b(4)}$ in which $R^{a(4)}$ and $R^{b(4)}$ independently represent H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkylC(O) or $R^{a(4)}$ and $R^{b(4)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_8 represents H, $(C_1$-$C_6)$alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_8 represents $(C_3$-$C_6)$cycloalkyl, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_3$-$C_6)$cycloalkoxy, aryl or heterocyclyl;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, $(C_1$-$C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or $(C_1$-$C_6)$alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I)

atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl or a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or (C_1-C_6)alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{15} represents aryl, heterocyclyl, one or more halogen (F, Cl, Br, I) atoms, (C_3-C_6)cycloalkyl, hydroxy(C_1-C_6)alkyl,(C_1-C_6)alkoxy, (C_3-C_6)cycloalkoxy, aryl, heterocyclyl or a group of formula $NR^{a(15)}R^{b(15)}$ in which $R^{a(15)}$ and $R^{b(15)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O), (C_1-C_6)alkoxyC(O) or $R^{a(15)}$ and $R^{b(15)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{16} is ethyl;

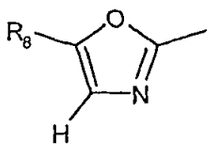
R^c represents an unsubstituted or monosubstituted or polysubstituted (C_1-C_4)alkylene group, (C_1-C_4)oxoalkylene group, (C_1-C_4)alkyleneoxy or oxy-(C_1-C_4)alkylene group, wherein any substituents each individually and independently are selected from (C_1-C_4)alkyl, (C_1-C_4)alkoxyl, oxy-(C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, carboxyl, carboxy-(C_1-C_4)alkyl, aryl, heterocyclyl, nitro, cyano, halogeno (F, Cl, Br, I), hydroxyl, $NR^{a(Rc)}R^{b(Rc)}$ in which $R^{a(Rc)}$ and $R^{b(Rc)}$ individually and independently from each other represents hydrogen, (C_1-C_4)alkyl or $R^{a(Rc)}$ and $R^{b(Rc)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine; Further R^c represents imino (-NH-), N-substituted imino (-NR_{19}-), (C_1-C_4)alkyleneimino or N-substituted (C_1-C_4)alkyleneimino (-$N(R_{19})$-$((C_1-C_4)$alkylene) wherein the mentioned alkylene groups are unsubstituted or monosubstituted or polysubstituted with any substituents according to above; and

R^d represents (C_3-C_8)cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, CN, NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halosubstituted (C_1-C_6)alkyl, $(C_3-$

C_6)cycloalkyl, aryl, heterocyclyl, (C_1-C_6)alkylsulfinyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylthio, (C_3-C_6)cycloalkylthio, arylsulfinyl, arylsulfonyl, arylthio, aryl(C_1-C_6)alkylthio, aryl(C_1-C_6)alkylsulfinyl, aryl(C_1-C_6)alkylsulfonyl, heterocyclyl(C_1-C_6)alkylthio, heterocyclyl(C_1-C_6)alkylsulfinyl, heterocyclyl(C_1-C_6)alkylsulfonyl, (C_3-C_6)cycloalkyl(C_1-C_6)alkylthio, (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfinyl or (C_3-C_6)cycloalkyl(C_1-C_6)alkylsulfonyl.

4. A compound according to claim 1 wherein;

R_1 represents $R_6OC(O)$, $R_{16}SC(O)$ or a group gII



(gII);

R_2 represents H or (C_1-C_6)alkyl optionally interrupted by oxygen and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_2 represents a group of formula $NR^{a(2)}R^{b(2)}$ in which $R^{a(2)}$ and $R^{b(2)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(2)}$ and $R^{b(2)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_3 represents H or a group of formula $NR^{a(3)}R^{b(3)}$ in which $R^{a(3)}$ and $R^{b(3)}$ independently represent H, (C_1-C_6)alkyl, (C_1-C_6)alkylC(O) or $R^{a(3)}$ and $R^{b(3)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_4 represents CN, halogen (F, Cl, Br, I), further R_4 represents (C_1-C_6)alkylC(O), (C_1-C_6)alkoxy wherein the alkoxygroup may optionally be substituted by one or more halogen (F, Cl, Br, I) atoms, OH and/or COOH and/or methoxycarbonyl;

R_5 represents H;

R_6 represents (C_1-C_{12})alkyl optionally interrupted by oxygen, (with the proviso that any such oxygen must be at least 2 carbon atoms away from the ester-oxygen connecting the R_6 group) and/or optionally substituted by OH, aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms; further R_6 represents (C_3-C_6)cycloalkyl or hydroxy(C_2-C_{12})alkyl;

R_8 represents H, $(C_1\text{-}C_6)$alkyl optionally interrupted by oxygen, and/or optionally substituted by aryl, cycloalkyl, heterocyclyl or one or more halogen (F, Cl, Br, I) atoms;

R_{14} represents H, OH with the proviso that the OH group must be at least 2 carbon atoms away from any heteroatom in the B ring/ring system, $(C_1\text{-}C_6)$alkyl optionally interrupted by oxygen and/or optionally substituted by one or more of OH, COOH and $COOR^e$; wherein R^e represents aryl, cycloalkyl, heterocyclyl or $(C_1\text{-}C_6)$alkyl optionally substituted by one or more of halogen (F, Cl, Br, I) atoms, OH, aryl, cycloalkyl and heterocyclyl; further R_{14} represents or a group of formula $NR^{a(14)}R^{b(14)}$ in which $R^{a(14)}$ and $R^{b(14)}$ independently represent H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylC(O), $(C_1\text{-}C_6)$alkoxyC(O) or $R^{a(14)}$ and $R^{b(14)}$ together with the nitrogen atom represent piperidine, pyrrolidine, azetidine or aziridine;

R_{15} represents H;

R_{16} is ethyl;

R^c represents an unsubstituted or monosubstituted $(C_1\text{-}C_4)$alkylene group, $(C_1\text{-}C_4)$alkyleneoxy or oxy-$(C_1\text{-}C_4)$alkylene group, wherein any substituents each individually and independently are selected from $(C_1\text{-}C_4)$alkyl; Further R^c represents imino (-NH-), N-substituted imino ($-NR_{19}$-);

R_{19} represents H or methyl;

R^d represents $(C_3\text{-}C_8)$cycloalkyl, aryl or heterocyclyl, and anyone of these groups optionally substituted with one or more halogen (F, Cl, Br, I) atoms and/or one or more of the following groups, CN, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halosubstituted $(C_1\text{-}C_6)$alkyl; and

X represents a single bond, imino (-NH-) or methylene ($-CH_2$-).

5. A compound according to claim 1 wherein;

R_1 is chosen from a group consisting of methoxycarbonyl, ethoxycarbonyl, (n-propyl)-oxycarbonyl, (iso-propyl)-oxycarbonyl, (iso-butyl)-oxycarbonyl, (tert-butyl)-oxycarbonyl, (2,2-dimethyl-propyl)-oxycarbonyl, (cyclo-propyl)-oxycarbonyl, (cyclo-butyl)-oxycarbonyl, (cyclo-pentyl)-oxycarbonyl, (2-hydroxyethyl)-oxycarbonyl), (2,2,2-trifluoroethyl)-oxycarbonyl, benzyl-oxycarbonyl, 4-fluorobenzyl-oxycarbonyl, ethylthiocarbonyl, and 5-ethyl-1,3-oxazol-2-yl;

R_2 is chosen from a group consisting of H, methyl, ethyl, isopropyl, and dimethylamino;

R_3 is chosen from a group consisting of H and amino;

R_4 is chosen from a group consisting of methoxy, chloro, cyano, (4-methoxy-4-oxobutoxy), (3-carboxy-propoxy) and methylcarbonyl;

Z represents O or is absent;

R_5 is H;

R_6 is chosen from a group consisting of methyl, ethyl, 2-hydroxyethyl, (2,2,2-trifluoroethyl), n-propyl, iso-propyl, cyclo-propyl, iso-butyl, tert-butyl, cyclo-butyl, 2,2-dimethylpropyl, cyclo-pentyl, benzyl and 4-fluorobenzyl;

R_8 is ethyl;

R_{14} is chosen from a group consisting of H, methyl, tert-butyloxycarbonyl-imino and amino;

R_{15} is H;

R_{16} is ethyl;

R^c is chosen from a group consisting of methylene ($-CH_2-$), methylmethylene ($-CH(CH3)-$), ethylene ($-CH_2CH_2-$), oxypropylene ($-OCH_2CH_2CH_2-$), imino (-NH-) and methylimino ($-N(CH_3)-$;

R_{19} is chosen from a group consisting of H and methyl;

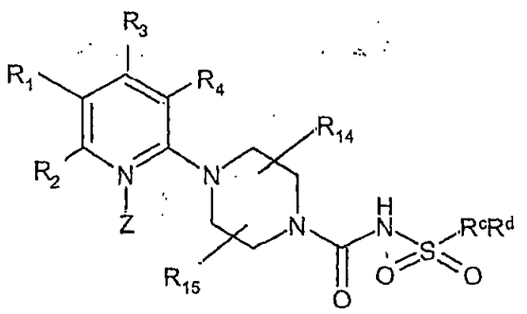
R^d is chosen from a group consisting of cyclopentyl, cyclohexyl, 4-methylcyclohexyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 4-ethylphenyl, 2-methoxycarbonyl-phenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 2-(trifluoromethyl)phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-cyanophenyl, 4-methoxyphenyl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 3,4-dichlorophenyl, 3,5-dichlorophenyl, 3,4-difluorophenyl, 2,5-dimethylphenyl, 3,5-dimethylphenyl, 4-isopropylphenyl, 3-fluoro-4-

methyl-phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, N-oxido-2-pyridyl, 6-[3-benzo[d]isoxazol-3-yl] and N-[(1,2-benzisoxazol-3-yl)];

X represents a single bond, imino (-NH-) or methylene (-CH_2-); and

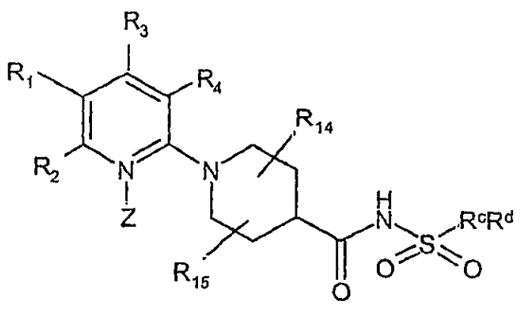
B is chosen from the group consisting of 4-piperazin-1-ylene, 4-piperidin-1-ylene, 3-piperidin-1-ylene, 3-azetidin-1-ylene, and the substituents R_{14} and R_{15} are connected to the B ring/ring system, in such a way that no quarternary ammonium compounds are formed (by these connections).

6. A compound according to any of claims 1-5 which is of the formula (Ia):



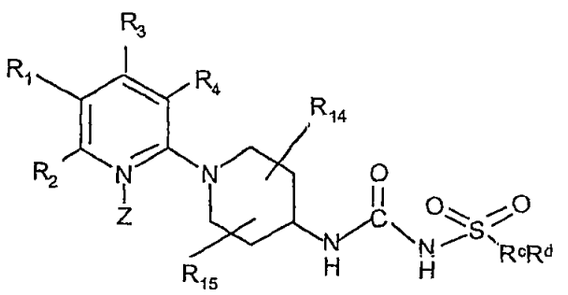
(Ia)

7. A compound according to any of claims 1-5 which is of the formula (Ib):



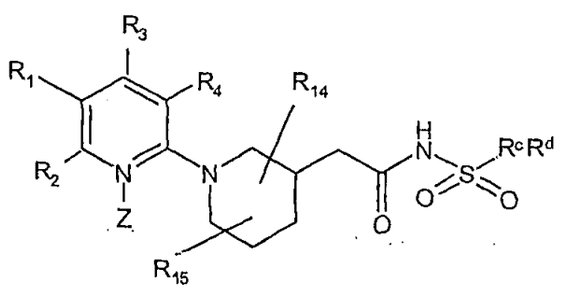
(Ib)

8. A compound according to any of claims 1-5 which is of the formula (Ic):



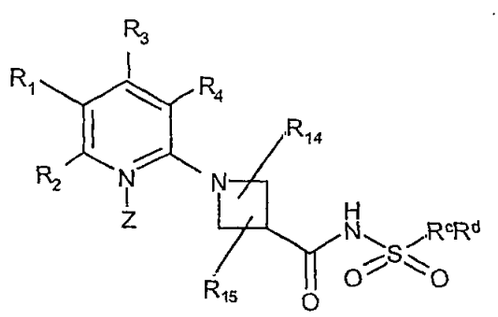
(Ic)

9. A compound according to any of claims 1-5 which is of the formula (Id):



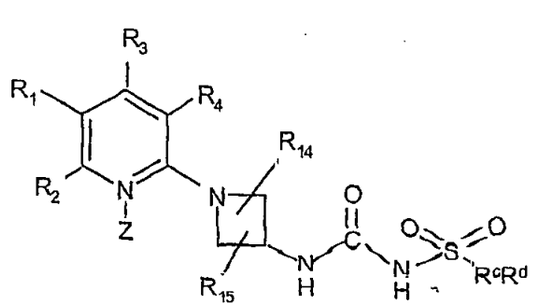
(Id)

10. A compound according to any of claims 1-5 which is of the formula (Ie):



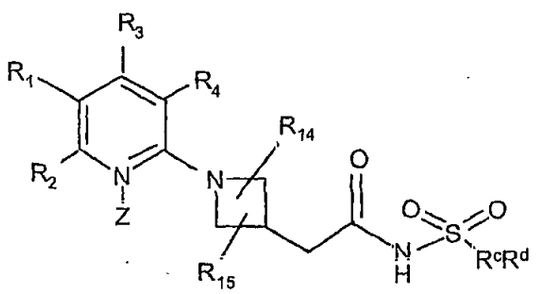
(Ie)

11. A compound according to any of claims 1-5 which is of the formula (If):



(If)

12. A compound according to any of claims 1-5 which is of the formula (Ig):



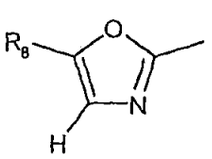
(Ig)

13. A compound according to any of claims 1-12 wherein Z is absent.

14. A compound according to any of claims 1-12 wherein Z is O.

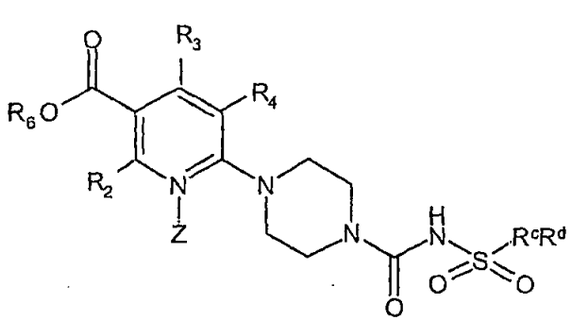
15. A compound according to any of claims 1-5 wherein R_1 represents $R_6OC(O)$.

16. A compound according to any of claims 1-5 wherein R_1 represents $R_{16}SC(O)$ or a group gII



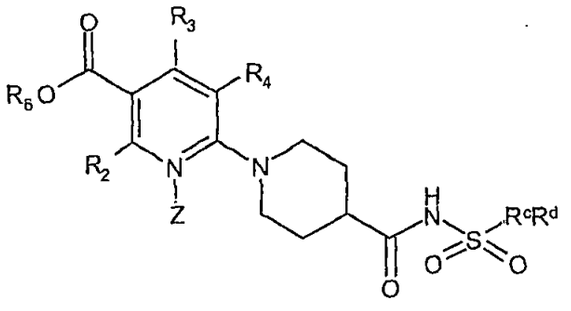
(gII).

17. A compound according to claim 15 which is of the formula (Iaa):



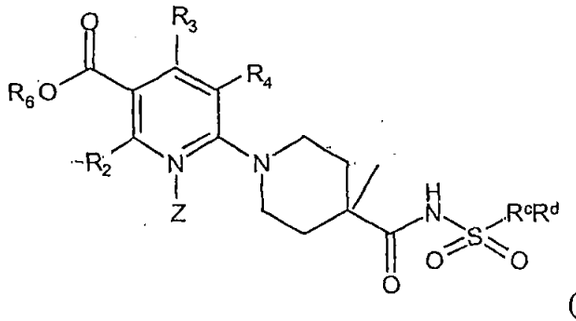
(Iaa).

18. A compound according to claim 15 which is of the formula (Ibb):



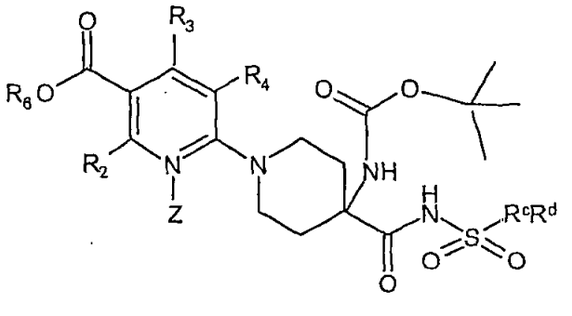
(Ibb).

19. A compound according to claim 15 which is of the formula (Ibc):



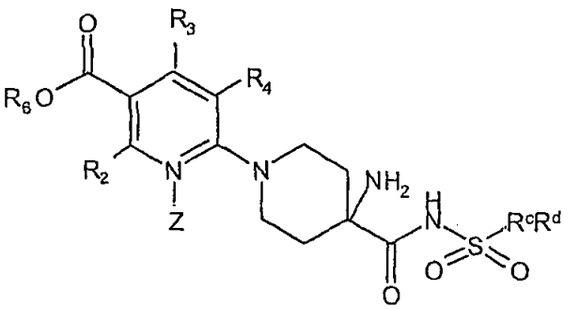
(Ibc).

20. A compound according to claim 15 which is of the formula (Ibd):



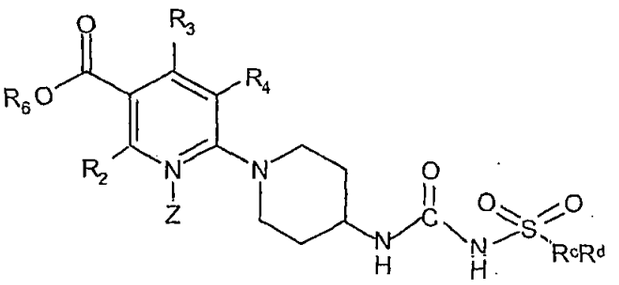
(Ibd).

21. A compound according to claim15 which is of the formula (Ibe):



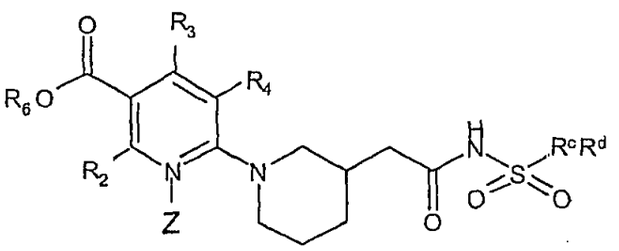
(Ibe).

22. A compound according to claim 15 which is of the formula (Icc):



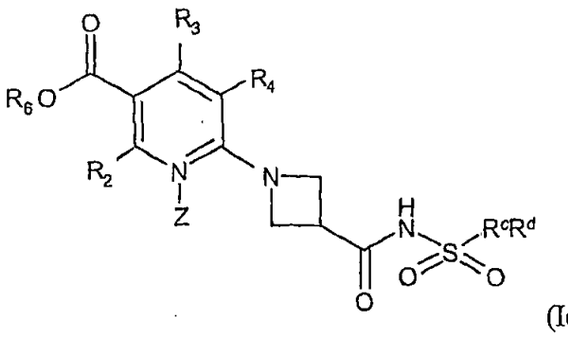
(Icc).

23. A compound according to claim 15 which is of the formula (Idd):



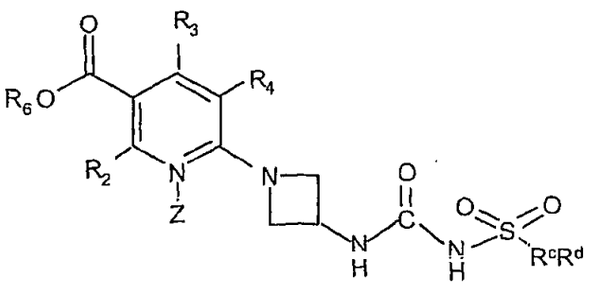
(Idd).

24. A compound according to claim15 which is of the formula (Iee):



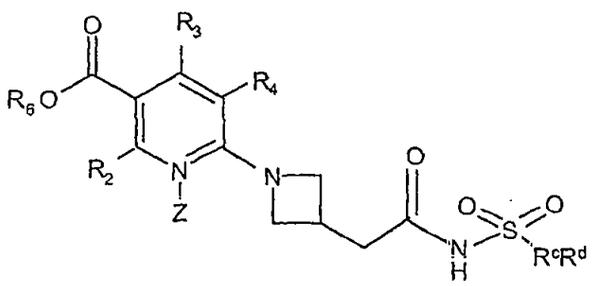
(Iee).

25. A compound according to claim15 which is of the formula (Iff):



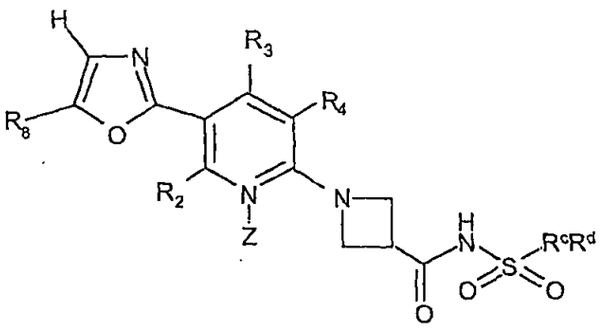
(Iff).

26. A compound according to claim 16 which is of the formula (Igg):



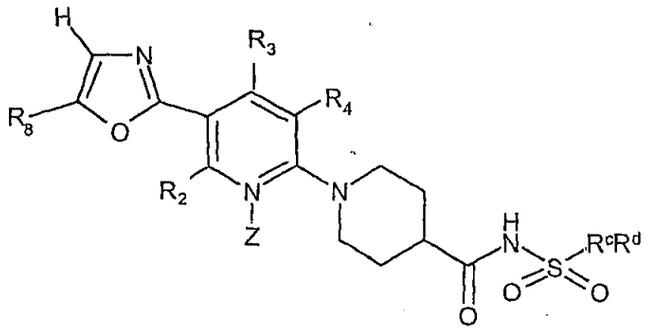
(Igg).

27. A compound according to claim 16 which is of the formula (Ihh):



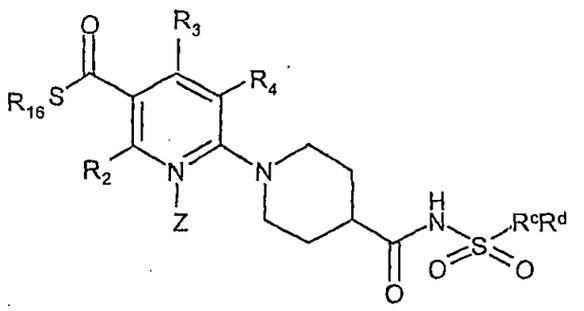
(Ihh).

28. A compound according to claim 16 which is of the formula (Iii):



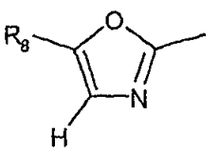
(Iii).

29. A compound according to claim 16 which is of the formula (Ijj):



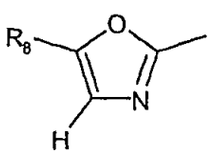
(Ijj).

30. A compound according to any of claims 1-5 wherein R_1 represents $R_6OC(O)$, $R_{16}SC(O)$ or a group gII



(gII).

31. A compound according to claim 30 wherein R_1 represents a group gII;



(gII).

32. A compound according to claim 30 wherein R_1 represents $R_{16}SC(O)$.

33. A compound selected from;

5-Cyano-6-[3-(2-methoxycarbonyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

6-[3-({[(3-Bromobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(2-nitro-phenylmethanesulfonylaminocarbonyl)-zetidin-1-yl]-nicotinic acid ethyl ester

6-[3-(2-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

6-[3-(4-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(4-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-6-[3-(3-fluoro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(3-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

6-[3-(3-Chloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

6-{3-[2-(3-Chloro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-5-cyano-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(4-nitro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(2-phenyl-ethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-(3-o-tolylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(3-nitro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-6-{3-[2-(4-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

5-Cyano-2-methyl-6-[3-(2-trifluoromethyl-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-nicotinic acid ethyl ester

5-Cyano-6-[3-(4-fluoro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-(3-cyclopentylmethanesulfonylaminocarbonyl-azetidin-1-yl)-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-{3-[2-(2-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-[3-(3,5-dichloro-phenylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-(3-cyclohexylmethanesulfonylaminocarbonyl-azetidin-1-yl)-2-methyl-nicotinic acid ethyl ester

5-Cyano-6-{3-[2-(3-fluoro-phenyl)-ethanesulfonylaminocarbonyl]-azetidin-1-yl}-2-methyl-nicotinic acid ethyl ester

6-[3-(Benzo[d]isoxazol-3-ylmethanesulfonylaminocarbonyl)-azetidin-1-yl]-5-cyano-2-methyl-nicotinic acid ethyl ester

1-[4-Amino-3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]-*N*-(benzylsulfonyl)piperidine-4-carboxamide

4-Amino-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloronicotic acid ethyl ester

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid isopropyl ester

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotinic acid tert-butyl ester

6-[3-({[(Benzylsulfonyl)amino]carbonyl}amino)azetidin-1-yl]-5-cyano-2-methylnicotic acid ethyl ester

6-(3-{2-[(Benzylsulfonyl)amino]-2-oxoethyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}-4-methylpiperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

N-(Benzylsulfonyl)-1-[3-chloro-5-(5-ethyl-1,3-oxazol-2-yl)pyridin-2-yl]piperidine-4-carboxamide

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid cyclopentyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid propyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-isopropylnicotinic acid ethyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-ethylnicotinic acid ethyl ester

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid 2,2-dimethylpropyl ester

N-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

6-(3-{[(Benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid isopropyl ester

5-Cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinic acid ethyl ester

6-[4-({[(4-Chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinic acid ethyl ester

6-(4-{[(Benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinic acid ethyl ester

N-[(1,2-Benzisoxazol-3-ylmethyl)sulfonyl]-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

N-(Benzylsulfonyl)-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]azetidine-3-carboxamide

N-[(4-Chlorobenzyl)sulfonyl]-1-[3-cyano-5-(5-ethyl-1,3-oxazol-2-yl)-6-methylpyridin-2-yl]piperidine-4-carboxamide

5-Cyano-2-methyl-6- (3-phenylmethanesulfonylaminocarbonyl-azetidin-1-yl)-nicotinic acid ethyl ester

ethyl 5-cyano-6-{3-[({[3-(4-methoxyphenoxy)propyl]sulfonyl}amino)carbonyl]azetidin-1-yl}-2-methylnicotinate

ethyl 4-amino-6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloronicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

2,2-dimethylpropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 6-[4-({[(3-bromobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

cyclopropyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-trifluoroethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-trifluoroethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

2,2,2-trifluoroethyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate

cyclopropyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

cyclobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

2-hydroxyethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

benzyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(3,4-dichlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-isopropylnicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-ethylnicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(1-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

propyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

isobutyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

isopropyl 5-cyano-2-methyl-6-{4-[({[4-(trifluoromethyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

isopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

isopropyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

isopropyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 6-[4-({[(3-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

isopropyl 6-[4-({[(2-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-{4-[({[2-(methoxycarbonyl)benzyl]sulfonyl}amino)carbonyl]piperidin-1-yl}-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-2-methyl-6-{4-[({[2-(2-methylphenyl)ethyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

4-{[2-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(4-methoxy-4-oxobutoxy)-2-methylnicotinate

ethyl 6-(4-{[(anilinosulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-{4-[({[methyl(phenyl)amino]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

isopropyl 5-cyano-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

isopropyl 5-cyano-6-[3-({[(3-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-2-methyl-6-[3-({[(2-phenylethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

isopropyl 5-cyano-6-[3-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-{3-[({[2-(methoxycarbonyl)benzyl]sulfonyl}amino)carbonyl]azetidin-1-yl}-2-methylnicotinate

isopropyl 5-cyano-6-[3-({[(2-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 6-[3-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-5-cyano-2-methylnicotinate

isopropyl 5-cyano-6-[3-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[3-({[(4-cyanobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

methyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

methyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

S-ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylpyridine-3-carbothioate

S-ethyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]pyridine-3-carbothioate

S-ethyl 6-[4-({[(4-chlorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-5-cyano-2-methylpyridine-3-carbothioate

S-ethyl 5-cyano-6-[4-({[(4-fluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylpyridine-3-carbothioate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-methoxy-2-methylnicotinate

ethyl 6-[4-({[(benzylsulfonyl)amino]carbonyl}amino)piperidin-1-yl]-5-cyano-2-methylnicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperazin-1-yl)-5-cyano-2-methylnicotinate

4-{[2-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-(ethoxycarbonyl)-6-methylpyridin-3-yl]oxy}butanoic acid

ethyl 5-cyano-2-methyl-6-{3-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]azetidin-1-yl}nicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-3-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-{4-[({[(1-oxidopyridin-2-yl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-3-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-4-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-2-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(3,5-dimethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

isopropyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(2,5-dimethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

benzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-{4-[({[(4-methylcyclohexyl)methyl]sulfonyl}amino)carbonyl]piperidin-1-yl}nicotinate

ethyl 5-cyano-6-[3-({[(4-isopropylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(2-phenylethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(pyridin-2-ylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(2,5-dimethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-chloro-2-methylnicotinate

ethyl 6-(3-{2-[(benzylsulfonyl)amino]-2-oxoethyl}azetidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(cyclopentylmethyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-(2-{[(4-fluorobenzyl)sulfonyl]amino}-2-oxoethyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(3-fluoro-4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-chloro-2-methylnicotinate

4-fluorobenzyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(3,4-difluorobenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[4-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-2-methyl-6-[4-({[(3-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-6-[3-({[(4-ethylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

ethyl 5-chloro-2-methyl-6-[3-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 5-cyano-6-[4-({[(3,4-difluorobenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]-2-methylnicotinate

ethyl 5-cyano-6-[3-({[(4-methoxybenzyl)sulfonyl]amino}carbonyl)azetidin-1-yl]-2-methylnicotinate

cyclopropyl 5-cyano-2-methyl-6-[4-({[(4-methylbenzyl)sulfonyl]amino}carbonyl)piperidin-1-yl]nicotinate

ethyl 5-cyano-2-methyl-6-[3-({[(pyridin-4-ylmethyl)sulfonyl]amino}carbonyl)azetidin-1-yl]nicotinate

ethyl 6-(3-{[(benzylsulfonyl)amino]carbonyl}azetidin-1-yl)-5-cyano-2-(dimethylamino)nicotinate

ethyl 6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate 1-oxide

ethyl 5-acetyl-6-(4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-2-methylnicotinate

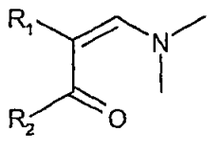
ethyl 6-{4-{[(benzylsulfonyl)amino]carbonyl}-4-[(tert-butoxycarbonyl)amino]piperidin-1-yl}-5-cyano-2-methylnicotinate

ethyl 6-(4-amino-4-{[(benzylsulfonyl)amino]carbonyl}piperidin-1-yl)-5-cyano-2-methylnicotinate;

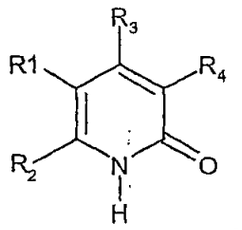
and pharmaceutically acceptable salts thereof.

34. A process for manufacturing a compound of formula (I) in which R_2, R_3, R_4, B, R_{14}, R_{15}, R^c and R^d are defined according to anyone of claims 1-5, R_1 is $R_6OC(O)$ wherein R_6 is defined according to anyone of claims 1-5, X is a single bond, Z is absent and R_5 is hydrogen, characterised in that the process comprises the following steps (I-vi);

i.) Reacting a compound of the formula $R_1CH_2C(O)R_2$, with dimethoxy-N,N-dimethylmethaneamine to form a compound of the formula



ii.) Reacting the compound from step i) with a compound of the general formula $R_4CH_2C(O)NH_2$ in an inert solvent such as ethanol in the presence of a strong base such as sodium ethoxide, to give a compound of the general formula



in which R_2, R_3, R_4, are defined according to anyone of claims 1-5, R_1 is $R_6OC(O)$ wherein R_6 is defined according to anyone of claims 1-5, and Z is absent.

iii) The product from step ii) is first washed with an alkaline water solution, e. g. a sodium bicarbonate solution and then washed with water whereafter the washed product is collected.

iv.) The compound from step iii) is reacted with a chlorinating agent such as thionyl chloride in an inert solvent, to give a compound of formula (VII) wherein L is a chlorine.

v.) reacting a compound of formula (X) with a compound of formula (III), in which B, R_{14}, R_{15}, R^c and R^d are defined according to anyone of claims 1-5, X is a single bond and R_5 is a hydrogen, while the compound of formula (III) is having the ring nitrogen protected by t-butyloxycarbonyl, in an inert organic solvent, in the presence of a coupling reagent and

optionally an organic base such as triethylamine or DIPEA, to give a compound of the general formula (VIII) after standard deprotection of the t-butyloxycarbonyl.

vi) The product from step v.) is reacted with the product from step iv.) in an inert solvent, optionally in the presence of an organic base such as triethylamine, to give a compound of formula (I) in which R_2, R_3, R_4, B, R_{14}, R_{15}, R^c and R^d are defined according to anyone of claims 1-4, R_1 is $R_6OC(O)$ and R_6 is defined according to anyone of claims 1-5, X is a single bond, Z is absent and R_5 is hydrogen.

35. The process according to Claim 34 wherein step iv.) comprises adding dimethylformamide to the reaction mixture.

36. The process according to Claim 35 wherein the inert solvent in step iv.) is toluene.

37. The process according to any of Claims 34-36 wherein the inert organic solvent in step v.) is THF.

38. The process according to any of Claims 34-37 wherein the coupling reagent in step v.) is TBTU.

39. The process according to any of Claims 34-38 wherein LiCl is added to the reaction mixture in step v.).

40. The process according to any of Claims 34-39 wherein step v.) comprises that the product is isolated by adding ammonia dissolved in water.

41. The process according to any of Claims 34-40 wherein the product from step vi) is purified and isolated by recrystallisation from ethyl acetate.

42. A pharmaceutical composition comprising a compound according to any one of claims 1-33 in combination with pharmaceutically acceptable adjuvants, diluents and/or carriers.

43. A compound according to any one of claims 1-33 for use in therapy.

44. Use of a compound according to any one of claims 1-33 for the manufacture of a medicament for treatment of platelet aggregation disorder.

45. Use of a compound according to any one of claims 1-33 for the manufacture of a medicament for the inhibition of the $P2Y_{12}$ receptor.

46. A method of treatment of a platelet aggregation disorder comprising administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to any of claims 1-33.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000832

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
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: C07D, A61K

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
EA	WO 2006073361 A1 (ASTRAZENECA AB), 13 July 2006 (13.07.2006)	1-46
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A	WO 2005035520 A1 (PORTOLA PHARMACEUTICALS, INC.), 21 April 2005 (21.04.2005), paragraph (0053), RN: 850340-20-4, 850340-19-1, 850340-21-5, 850340-22-6	1-46
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A	WO 2004106305 A1 (ASTRAZENECA AB), 9 December 2004 (09.12.2004), page 65, line 10 - page 67, line 3, abstract, RN: 803736-15-4	1-46
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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2006	04 -10- 2006

Name and mailing address of the ISA/	Authorized officer
Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Helena Melander/MP Telephone No. +46 8 782 25 00

2/2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000832

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.: 46
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 46 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

WO	2006073361	A1	13/07/2006	GB	0500140	D	00/00/0000
				GB	0521484	D	00/00/0000
WO	2005035520	A1	21/04/2005	AU	2004279809	A	21/04/2005
				CA	2539882	A	21/04/2005
				EP	1667989	A	14/06/2006
				US	20050113399	A	26/05/2005
WO	2004106305	A1	09/12/2004	AU	2004242626	A	09/12/2004
				BR	PI0410933	A	27/06/2006
				CA	2526884	A	09/12/2004
				EP	1633717	A	15/03/2006
				GB	0312609	D	00/00/0000
				IS	8190	A	21/12/2005
				MX	PA05012883	A	22/02/2006
				NO	20060001	A	02/03/2006
				RU	2005136130	A	27/06/2006
				AU	2003280904	A	00/00/0000
				EP	1559085	A	03/08/2005
				SE	0301700	D	00/00/0000
EP	1466912	A1	13/10/2004	CA	2472711	A	31/07/2003
				US	20050153977	A	14/07/2005
				CN	1639157	A	13/07/2005
				WO	03062233	A	31/07/2003
WO	0157037	A1	09/08/2001	AT	309999	T	15/12/2005
				AU	3664401	A	14/08/2001
				CA	2400479	A	09/08/2001
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				DK	1257550	T	27/03/2006
				EP	1257550	A,B	20/11/2002
				SE	1257550	T3	
				ES	2252193	T	16/05/2006
				JP	2003522177	T	22/07/2003
				US	6689786	B	10/02/2004
				US	6906063	B	14/06/2005
				US	7022731	B	04/04/2006
				US	7056926	B	06/06/2006
				US	20020025961	A	28/02/2002
				US	20020077486	A	20/06/2002
				US	20030162774	A	28/08/2003
				US	20040147576	A	29/07/2004
				US	20050228029	A	13/10/2005

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

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Oficina Internacional

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18 de enero de 2007 (18.01.2007)

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A61K 31/4427 (2006.01) *C07D 401/14* (2006.01)
A61K 31/4439 (2006.01) *C07D 413/14* (2006.01)
A61K 31/4545 (2006.01)

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

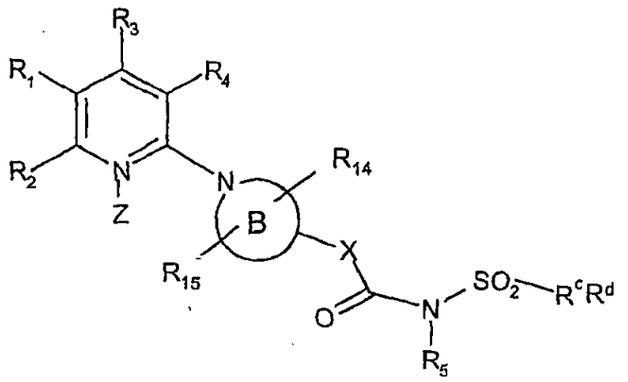
(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:
— *con informe internacional de búsqueda*

Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.

(54) Título: NOVEDOSOS ANÁLOGOS DE PIRIDINA



(I)

(57) Extracto: La presente invención se refiere a ciertos análogos novedosos de piridina de Fórmula (I), a procesos para preparar tales compuestos, a su utilidad como inhibidores de $P2Y_{12}$ y como agentes anti-trombóticos etc., a su uso como medicamentos en enfermedades cardiovasculares, así como a composiciones farmacéuticas que los contienen.

WO 2007/008140 A1

NOVEDOSOS ANÁLOGOS DE PIRIDINA

Campo de la invención

La presente invención provee compuestos novedosos de piridina, su uso como medicamentos, composiciones que los contienen y procesos para su preparación.

Antecedentes de la invención

La adhesión y agregación plaquetaria son episodios iniciadores en la trombosis arterial. Aunque el proceso de la adhesión plaquetaria a la superficie sub-endotelial puede tener un papel importante que jugar en la reparación de las paredes de vasos dañados, la agregación plaquetaria que esto inicia puede precipitar la oclusión trombótica aguda de lechos vasculares vitales, llevando a episodios con alta morbilidad tal como infarto del miocardio y angina inestable. El éxito de intervenciones utilizadas para prevenir o aliviar estas enfermedades, tales como trombólisis y angioplastia se ve también afectado por la oclusión o re-oclusión mediada por plaquetas.

La hemostasis se controla mediante un estricto balance entre agregación plaquetaria, coagulación y fibrinólisis. La formación de trombos bajo condiciones patológicas, como por ejemplo ruptura de la placa arteriosclerótica, se inicia primeramente por adhesión, activación y agregación plaquetaria. Esto resulta no sólo en la formación de un tapón plaquetario, sino también en la exposición de fosfolípidos cargados negativamente en la membrana plaquetaria externa, promoviendo la coagulación sanguínea. Se esperaría que la inhibición de la acumulación del tapón plaquetario inicial reduzca la formación de trombos y disminuya el número de episodios cardiovasculares, como se demostró por el efecto antitrombótico, por ejemplo, de la aspirina (BMJ 1994; 308: 81-106 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients.). La activación/agregación plaquetaria puede inducirse por una

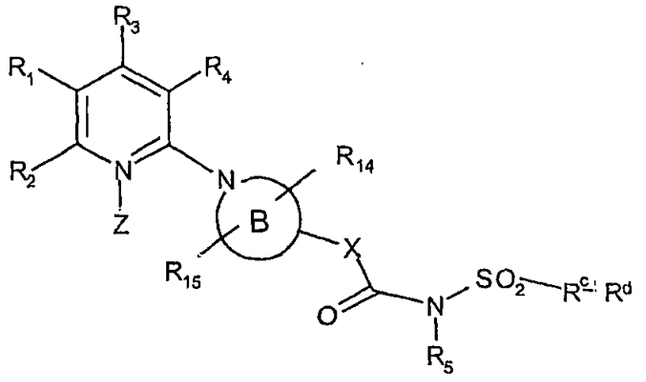
variedad de diferentes agonistas. No obstante, tienen que activarse distintas vías señalizadoras intracelulares para obtener una completa agregación plaquetaria, mediada por proteínas G G_q, $G_{12/13}$ y G_i (Platelets, AD Michelson ed., Elsevier Science 2002, ISBN 0-12-493951-1; 197-213: D Woulfe, et al. Signal transduction during the initiation, extension, and perpetuation of platelet plug formation). En las plaquetas, el receptor $P2Y_{12}$ acoplado a la proteína G (conocido también previamente como el receptor P_{2T}, $P2T_{ac}$, o $P2Y_{cyc}$ plaquetario) señala mediante G_i, resultando en una disminución de cAMP intracelular y una agregación completa (Nature 2001; 409: 202-207 G Hollopeter, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs.). ADP liberado de gránulos densos reaccionará positivamente sobre el receptor $P2Y_{12}$ para permitir la agregación completa.

Evidencia clínica del papel clave del mecanismo de retroalimentación ADP-$P2Y_{12}$ es aportada por el uso clínico de clopidogrel, un profármaco de tienopiridina cuyo metabolito activo se une selectiva e irreversiblemente al receptor $P2Y_{12}$, que ha demostrado en varios estudios clínicos su efectividad en reducir el riesgo de episodios cardiovasculares en pacientes en peligro (Lancet 1996; 348: 1329-39: CAPRIE Steering committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE); N Engl J Med 2001; 345 (7): 494-502): The Clopidogrel in Unstable Angina to prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.). En estos estudios, el beneficio clínico con un riesgo reducido de hemorragia se compara con tienopiridinas (Sem Thromb Haemostas 2005; 31 (2): 195-204 JJJ van Giezen & RG Humphries. Preclinical and clinical studies with selective reversible direct $P2Y_{12}$ antagonists).

Por consiguiente, es un objeto de la presente invención proveer antagonistas reversibles y selectivos de $P2Y_{12}$ como agentes antitrombóticos.

Sumario de la invención

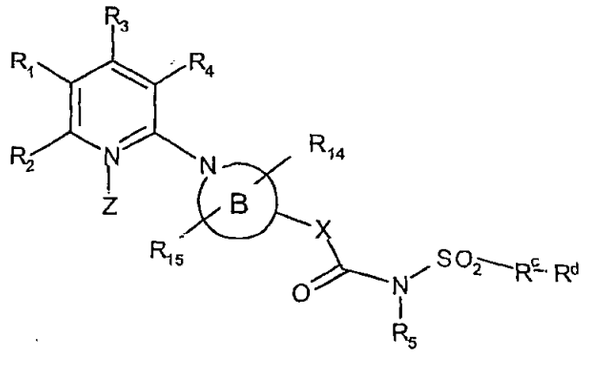
Sorpresivamente hemos descubierto ahora que ciertos compuestos de piridina de fórmula (I) o su sal farmacéuticamente aceptable son antagonistas reversibles y selectivos de $P2Y_{12}$, denominados a partir de ahora los compuestos de la invención. Inesperadamente, los compuestos de la invención exhiben propiedades benéficas que los hacen particularmente apropiados para uso en el tratamiento de enfermedades/afecciones como se describe a continuación (véase página 87). Ejemplos de tales propiedades benéficas son potencia elevada, alta selectividad y un margen terapéutico ventajoso.



(I)

Descripción detallada de la invención

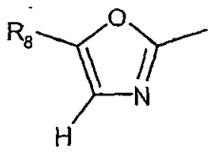
De acuerdo con la presente invención se provee un compuesto novedoso de fórmula (I) o su sal farmacéuticamente aceptable:



(I)

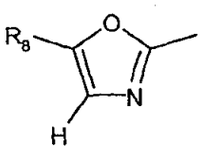
en donde

R_1 representa $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ o un grupo gH



(gII),

preferiblemente R_1 representa $R_6OC(O)$, $R_{16}SC(O)$ o el grupo gH;



(gII).

R_2 representa H, CN, halógeno (F, Cl, Br, I), NO_2, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_{12})alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(2)}R^{b(2)}$ en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Además, R_1 + R_2 juntos (con dos átomos de carbono del anillo piperidina) pueden formar una lactona cíclica de 5 ó 6 miembros;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_3 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(3)}R^{b(3)}$ en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, COOH, (C_1-C_6)alcoxicarbonilo, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_4 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquilcicloalquilo, (C_1-C_{12})alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH y/o COOH y/o (C_1-C_6)alcoxicarbonilo; además R_4 representa (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-

C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(4)}R^{b(4)}$ en la cual $R^{a(4)}$ y $R^{b(4)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(4)}$ y $R^{b(4)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Z representa O o está ausente;

R_5 representa H o (C_1-C_{12})alquilo;

R_6 representa (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno, (con la salvedad que cualquier oxígeno tal tiene que estar por lo menos 2 átomos de carbono alejado del éster-oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_6 representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_{12})alquilo, arilo o heterociclilo;

R_7 representa (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_7 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, arilo o heterociclilo;

R_8 representa H, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_8 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-

C_6)cicloalquil(C_1-C_{12})alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo;

R_{14} representa H, OH con la salvedad que el grupo OH tiene que estar por lo menos 2 átomos de carbono alejado de cualquier heteroátomo en el anillo B/sistema de anillo, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más de OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_{12})alquilo sustituido opcionalmente por uno o más de átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_12)alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo, un grupo de fórmula $NR^{a(14)}R^{b(14)}$ en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más de OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_{12})alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{15} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-

C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(15)}R^{b(15)}$ en la cual $R^{a(15)}$ y $R^{b(15)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O)), (C_1-C_{12})alcoxiC(O) o $R^{a(15)}$ y $R^{b(15)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{16} representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{16} representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{17} representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{17} representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{18} representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{18} representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido o polisustituido, un grupo (C_1-C_4)oxoalquileno, un grupo (C_1-C_4)alquilenoxi o un grupo oxi-(C_1-C_4)alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de

(C_1-C_4)alquilo, (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido, (C_1-C_4)alquilenimino o (C_1-C_4)alquilenimino (-N(R_{19})-((C_1-C_4)alquileno) N-sustituido, en donde los mencionados grupos alquileno son no sustituidos, o monosustituidos o polisustituidos con cualesquiera sustituyentes de acuerdo con lo anterior; preferiblemente R^c representa imino o (C_1-C_4)alquilenimino o un grupo (C_1-C_4)alquileno o un grupo (C_1-C_4)oxoalquileno no sustituido o monosustituido o polisustituido con cualesquiera sustituyentes de acuerdo con lo anterior;

R_{19} representa H o (C_1-C_4)alquilo;

R^d representa (C_3-C_8)cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, (C_1-C_{12})alquilo, (C_1-C_{12})alcoxiC(O), (C_1-C_{12})alcoxi, (C_1-C_{12})alquilo halógeno sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(Rd)}R^{b(Rd)}$ en la cual $R^{a(Rd)}$ y $R^{b(Rd)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(Rd)}$ y $R^{b(Rd)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

X representa un enlace simple, imino (-NH-), metileno (-CH_2-), iminometileno (-CH_2-NH-) en donde el carbono se conecta al anillo B/sistema de anillo, metilenimino (-NH-CH_2-) en donde el nitrógeno se conecta al anillo B/sistema de anillo y cualquier carbono y/o nitrógeno en estos grupos puede sustituirse opcionalmente con (C_1-C_6) alquilo; además X puede representar un grupo (-CH_2-)n en donde n= 2-6, que opcionalmente es insaturado y/o se sustituye por uno o más sustituyentes seleccionados entre halógeno, hidroxilo o (C_1-C_6)alquilo;

B es un anillo/sistema de anillo de 4 a 11 miembros, monocíclico o bicíclico, que comprende uno o más átomos de nitrógeno y, opcionalmente, uno o más átomos seleccionados de oxígeno o azufre, el cual nitrógeno se conecta al anillo piridina (de acuerdo con fórmula I) y, además, el anillo B/sistema de anillo se conecta a X en otra de sus posiciones. Los sustituyentes R_{14} y R_{15} se conectan al anillo B/sistema de anillo de tal manera que no se forman compuestos de amonio cuaternario (mediante estas conexiones).

Valores preferidos de cada grupo variable son los siguientes. Tales valores pueden usarse donde sea apropiado con cualquiera de los valores, definiciones, reivindicaciones, aspectos o incorporaciones definidos más arriba o más adelante en el texto. En particular, cada uno puede usarse como una limitación individual a la definición más amplia de fórmula (I).

Para evitar dudas hay que entender que, donde en esta especificación se califica un grupo con 'definido más arriba', 'definido anteriormente' o 'ya

Se entenderá que cuando compuestos de fórmula I contienen un centro quiral, los compuestos de la invención pueden existir, y aislarse, en forma racémica u ópticamente activa. La invención incluye cualquier forma racémica u ópticamente activa de un compuesto de fórmula I, que actúe como antagonista de receptor $P2Y_{12}$. La síntesis de formas ópticamente activas puede llevarse a cabo por técnicas estándar de química orgánica bien conocidas en el arte, por ejemplo, mediante resolución de una mezcla racémica, cromatografía quiral, síntesis de materiales de partida ópticamente activos o mediante síntesis asimétrica.

Se entenderá igualmente que los compuestos de la fórmula I pueden exhibir el fenómeno de tautomerismo; la presente invención incluye cualquier forma tautomérica de un compuesto de fórmula I, que es un antagonista de receptor $P2Y_{12}$.

Se entenderá asimismo que, en la medida en que compuestos de la presente invención existan como solvatos y, en particular, hidratos, éstos se incluyen como parte de la presente invención.

Hay que entender también que términos genéricos tales como "alquilo" incluyen los grupos de cadena recta y los grupos de cadena ramificada, tales como butilo y *terc*-butilo. No obstante, cuando se utiliza un término específico tal como "butilo", éste es específico para el grupo butilo "normal" o de cadena recta, mencionándose específicamente isómeros de cadena recta tales como "t-butilo" en forma expresa.

En una incorporación alquilo no se sustituye o se sustituye por uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, (C_1-C_{12})alquilo, (C_1-C_{12})alcoxiC(O), (C_1-C_{12})alcoxi, (C_1-C_{12})alquilo halógeno sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio,

aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula NR^aR^b en la cual R^a y R^b representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o R^a y R^b junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina.

El término "alquilo" incluye grupos de cadena lineal o ramificada, sustituidos opcionalmente por uno o más halógenos (F, Cl, Br, I) o átomos de halógeno mixtos.

Una incorporación de alquilo cuando se sustituye por uno o más átomos de halógeno (F, Cl, Br, I) es, por ejemplo, alquilo sustituido por uno o más átomos de flúor. Otra incorporación de alquilo halógeno sustituido incluye grupos perfluoroalquilo tales como trifluorometilo.

El término "cicloalquilo" denota generalmente un hidrocarburo cíclico (C_3-C_6) sustituido o no sustituido, a menos que se especifique otra longitud de cadena.

En una incorporación cicloalquilo se sustituye por uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, (C_1-C_{12})alquilo, (C_1-C_{12})alcoxiC(O), (C_1-C_{12})alcoxi, (C_1-C_{12})alquilo halógeno sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula NR^aR^b en la cual R^a y R^b

representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o R^a y R^b junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina.

El término "alcoxi" incluye grupos de cadena lineal o ramificada, sustituidos opcionalmente por uno o más halógenos (F, Cl, Br, I) o átomos de halógeno mixtos.

El término arilo denota un hidrocarburo aromático (C_6-C_{14}) sustituido o no sustituido e incluye, pero no se limita a, fenilo, naftilo, tetrahidronaftilo, indenilo, indanilo, antracenilo, fenantrenilo, y fluorenilo.

En una incorporación arilo se sustituye por uno o más átomo de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, (C_1-C_{12})alquilo, (C_1-C_{12})alcoxiC(O), (C_1-C_{12})alcoxi, (C_1-C_{12})alquilo halógeno sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula NR^aR^b en la cual R^a y R^b representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o R^a y R^b junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina.

El término "heterociclilo" denota un sistema de anillo monocíclico o multicíclico de 4 a 10 miembros, sustituido o no sustituido, en el cual uno o más de los átomos en el anillo o anillos es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, especialmente grupos heterocíclicos alifáticos o aromáticos de 4, 5 ó 6 miembros, e incluye, pero no se limita a grupos azetidina, furano, tiofeno, pirrol, pirrolina, pirrolidina,

dioxolano, oxatiolano, oxazolano, oxazol, tiazol, imidazol, imidazolina, imidazolidina, pirazol, pirazolina, pirazolidina, isotiazol, oxadiazol, furazano, triazol, tiadiazol, pirano, piridina, así como piridin-N-óxido, piperidina, dioxano, morfolina, ditiano, oxatiano, tiomorfolina, piridazina, pirimidina, pirazina, piperazina, triazina, tiadiazina, ditiazina, azaindol, azaindolina, indol, indolina, naftiridina, benzoxadiazol, dihidrobenzodioxina, benzotiofeno, benzotiadiazol, imidazotiazol, 2,3-dihidrobenzofurano, isoxazol, 3-benzisoxazol, 1,2-benzisoxazol, dihidropirazol, y se entenderá que incluyen todos los isómeros de los grupos ya identificados. Para los grupos anteriores, por ejemplo, azetidinilo, el término "azetidinilo" así como "azetidinileno", etc., se entenderá que incluye todos los posibles regioisómeros. Hay que entender además que el término heterociclilo puede quedar comprendido por una selección entre las posibles incorporaciones dadas para una variable e incluido por otra (o la misma) selección para otra variable, por ejemplo R_4, cuando se selecciona como heterociclilo puede ser un furano, cuando R^d (también cuando se selecciona como heterociclilo) puede ser un pirrol.

En una incorporación heterociclilo se sustituye por uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, $(C_1$-$C_{12})$alquilo, $(C_1$-$C_{12})$alcoxiC(O), $(C_1$-$C_{12})$alcoxi, $(C_1$-$C_{12})$alquilo halógeno sustituido, $(C_3$-$C_6)$cicloalquilo, arilo, heterociclilo, $(C_1$-$C_{12})$alquilsulfinilo, $(C_1$-$C_{12})$alquilsulfonilo, $(C_1$-$C_{12})$alquiltio, $(C_3$-$C_6)$cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril$(C_1$-$C_{12})$alquiltio, aril$(C_1$-$C_{12})$alquilsulfinilo, aril$(C_1$-$C_{12})$alquilsulfonilo, heterociclil$(C_1$-$C_{12})$alquiltio, heterociclil$(C_1$-$C_{12})$alquilsulfinilo, heterociclil$(C_1$-$C_{12})$alquilsulfonilo, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_{12})$alquiltio, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_{12})$alquilsulfinilo, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_{12})$alquilsulfonilo o un grupo de fórmula NR^aR^b en la cual R^a y R^b representan independientemente H, $(C_1$-$C_{12})$alquilo, $(C_1$-$C_{12})$alquilC(O) o R^a y R^b junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina.

En otra incorporación de la invención el grupo heterociclilo comprende un anillo heterocíclico de 5 ó 6 miembros, aromático, que contiene uno, dos o tres heteroátomos seleccionados de nitrógeno, oxígeno y azufre, y un anillo heterocíclico de 5 ó 6 miembros, aromático, que contiene uno, dos o tres heteroátomos seleccionados de nitrógeno, oxígeno y azufre, que se fusiona a un anillo benceno.

En una incorporación alternativa de la invención el grupo heterociclilo es un anillo heterocíclico de 5 ó 6 miembros, no aromático, que contiene uno, dos o tres heteroátomos seleccionados de nitrógeno, oxígeno y azufre, fusionado a un anillo benceno.

En una incorporación adicional de la invención el grupo heterociclilo es un grupo seleccionado entre furilo, pirrolilo, tienilo, piridilo, N-óxido-piridilo, pirazinilo, piridinilo, piridazinilo, imidazolilo, oxazolilo, isooxazolilo, tiazolilo, isotiazolilo, oxadiazolilo, 1,2,3-triazolilo, 1,2,4-triazolilo, benzfuranilo, quinolilo, isoquinolilo, benzimidazolilo, indolilo, benzdihidrofuranilo, benzodioxolilo (tal como 1,3-benzodioxolilo), benzoxadiazol, dihidrobenzodioxina, benzotiofeno, benzotiadiazol, imidazotiazol, 2,3-dihidrobenzofurano, isoxazol, dihidropirazol y benzdioxanilo (tal como 1,4-benzdioxanilo). Valores más particulares incluyen, por ejemplo, furilo, pirrolilo, tienilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, benzoxadiazol, dihidrobenzodioxina, benzotiofeno, benzotiadiazol, imidazotiazol, 2,3-dihidrobenzofurano, isoxazol, 1,2-benzisoxazol, dihidropirazol y benzdioxanilo (tal como 1,4-benzdioxanilo).

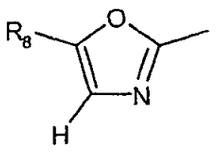
En todavía otra incorporación de la invención el grupo heterociclilo es un grupo seleccionado entre furilo, pirrolilo, tienilo, piridilo, N-óxido-piridilo, pirazinilo, pirimidinilo, piridazinilo, benzoxadiazol,

dihidrobenzodioxina, benzotiofeno, benzotiadiazol, imidazotiazol, 2,3-dihidrobenzofurano, isoxazol, 1,2-benzisoxazol o dihidropirazol.

En una incorporación de la invención R_1 representa $R_6OC(O)$.

En otra incorporación de la invención R_1 representa $R_{16}SC(O)$.

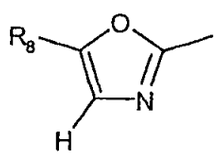
En todavía otra incorporación R_1 representa un grupo (gII),



(gII),

En una incorporación adicional de la invención R_1 se selecciona entre $R_6OC(O)$ y $R_{16}SC(O)$ en donde R_6 puede ser metilo, etilo, 2-hidroxietilo, 2,2,2-trifluoroetilo, isopropilo, ciclo-propilo, iso-butilo, n-butilo, ciclo-butilo, n-propilo, *terc*-butilo, ciclo-pentilo, 2,2-dimetilpropilo, bencilo y 4-fluorobencilo y en donde R_{16} es etilo.

R_1 puede estar comprendido también por un grupo gII,



(gII),

en la cual R_8 se selecciona de H, $(C_1\text{-}C_6)$alquilo, tal como metilo o etilo.

En otra incorporación para el grupo R_8, este grupo puede seleccionarse entre hidrógeno, metilo, etilo, n-propilo y n-butilo.

Incorporaciones para R_2 incluyen, por ejemplo, H, y $(C_1\text{-}C_4)$alquilo. Otras incorporaciones para R_2 son metilo, etilo, iso-propilo, fenilo, metoxi, o amino no sustituido o sustituido opcionalmente con metilo.

Incorporaciones para R_3 incluyen, por ejemplo, H, metilo, metilsulfinilo, hidroximetilo, metoxi o amino no sustituido o sustituido opcionalmente con uno o dos grupos metilo.

Otras incorporaciones para R_3 incluyen H o amino no sustituido o sustituido opcionalmente con uno o dos grupos metilo.

Incorporaciones para R_4 incluyen H, halógeno tal como cloro, metilo, ciano, nitro, amino no sustituido o sustituido opcionalmente con uno o dos grupos metilo y, además, incluye 4-metoxi-4-oxobutoxi, 3-carboxi-propoxi y metilcarbonilo.

En una incorporación de la invención Z está ausente.

En otra incorporación de la invención Z representa O.

En una incorporación R_5 representa hidrógeno o metilo. En otra incorporación R_5 es hidrógeno.

Otras incorporaciones R_8 incluyen hidrógeno, metilo y etilo.

Otras incorporaciones R_{14} incluyen, por ejemplo, hidrógeno, metilo, amino, *terc*-butoxicarbonilo, *terc*-butiloxicarbonil-imino, 2-carboxietilo y 3-*terc*-butoxi-3-oxo-propilo.

Otras incorporaciones R_{14} incluyen, por ejemplo, hidrógeno, metilo, *terc*-butiloxicarbonil-imino, y amino.

En una incorporación de la invención R_{15} representa H.

Otras incorporaciones de R^d incluyen arilo o heterociclilo, más particularmente, arilo o heterociclilo aromático.

Otra incorporación para R^d incluye arilo tal como fenilo y heterociclilo aromático tal como tienilo.

Otras incorporaciones de R^d incluyen fenilo, el cual puede sustituirse opcionalmente.

En una incorporación especial R^d representa arilo, heterociclilo o (C_3-C_6)cicloalquilo, y cualquiera de estos grupos se sustituyen opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) o átomos de halógeno mixtos, y/o uno o más de los siguientes grupos, OH, CN, NO_2, (C_1-C_{12})alquilo, (C_1-C_{12})alcoxiC(O), (C_1-C_{12})alcoxi, (C_1-C_{12})alquilo halógeno sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_12)alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(Rd)}R^{b(Rd)}$ en la cual $R^{a(Rd)}$ y $R^{b(Rd)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(Rd)}$ y $R^{b(Rd)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Aún otras incorporaciones para R^d incluyen fenilo opcionalmente sustituido en las posiciones 2, 3, 4 ó 5, así como cualquier combinación de las mismas. Ejemplos de sustituyentes son ciano, tetrazol-5-ilo, metoxi, trifluorometoxi, metilo, trifluorometilo, fluoro, cloro, bromo, metilsulfonilo, nitro, 3-metil-5-oxo-4,5-dihidro-1*H*-pirazol-1-ilo. Dos posiciones adyacentes (por ejemplo, 2, 3) pueden conectarse asimismo para formar un anillo. Un ejemplo de tal sustituyente es 2-naftilo. Valores adicionales más

específicos para heteroarilos son 2-cloro-5-tienilo, 3-bromo-5-cloro-2-tienilo, 2,1,3-benzoxadiazol-4-ilo, 2,4-dimetil-1,3-tiazol-5-ilo, 2,3-dihidro-1,4-benzodioxin-6-ilo, 5-cloro-3-metil-1-benzotien-2-ilo, 2,1,3-benzotiadiazol-4-ilo, 2,5-dimetil-3-furilo, 6-cloroimidazo[2,1-5][1,3] tiazo-5-ilo, 2,3-dihidro-1-benzofuran-5-ilo, 5-cloro-3-tienilo, 5-isoxazo-5-il-2-tienilo, 5-isoxazol-3-il-2-tienilo, 4-bromo-5-cloro-2-tienilo, 5-bromo-6-cloropiridin-3-ilo, 5-bromo-2-tienilo, 5-piridin-2-il-2-tienilo, 2,5-dicloro-3-tienilo, 4,5-dicloro-2-tienilo, benzotien-3-ilo, 2,5-dimetil-3-tienilo, 3-tienilo, 2-tienilo, 5-metilisoxazol-4-ilo, piridin-3-ilo, [1-metil-5-(trifluorometil)-1*H*-pirazol-3-il]-2-tienilo, 5-cloro-1,3-dimetil-1*H*-pirazol-4-ilo, 4-[(4-clorofenil)sulfonil]-3-metil-2-tienilo, 5-(metoxicarbonil)-2-furilo y 4-(metoxicarbonil)-5-metil-2-furilo.

En una incorporación de la invención R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido o disustituido en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina, y R^d representa arilo, es decir, R^cR^d representa un grupo aril-(C_1-C_4)alquileno con cualesquiera sustituyentes de acuerdo con lo anterior.

En una incorporación preferida de la invención R^c representa un grupo (C_1-C_3)alquileno no sustituido o monosustituido o disustituido en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e

independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina , y R^d representa arilo, es decir, R^cR^d representa un grupo aril-(C_1-C_3)alquileno con cualesquiera sustituyentes de acuerdo con lo anterior.

En una incorporación adicional de la invención R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido o disustituido en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1- C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina, y R^d representa heterociclilo, es decir, R^c R^d representa un grupo heterociclil-(C_1-C_4)alquileno con cualesquiera sustituyentes de acuerdo con lo anterior.

En una incorporación adicional preferida de la invención R^c representa un grupo (C_1-C_3)alquileno no sustituido o monosustituido o disustituido en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxi, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina, y R^d representa heterociclilo, es decir, R^c R^d representa un grupo heterociclil-(C_1-C_3)alquileno con cualesquiera sustituyentes de acuerdo con lo anterior.

En una incorporación particular de la invención R^c representa un grupo C_1-alquileno en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxi, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina, y R^d representa arilo, es decir, R^cR^d representa un grupo aril-C_1-alquileno con cualesquiera sustituyentes de acuerdo con lo anterior.

En una incorporación de la invención R_{19} representa hidrógeno.

En otra incorporación de la invención R_{19} representa metilo.

En una muy particular incorporación de la invención R^cR^d representa un grupo bencilo, o un grupo bencilo que se sustituye de acuerdo con lo que se describe en conexión con la sustitución del grupo arilo.

En una incorporación de la invención X representa un enlace simple.

En otra incorporación de la invención X representa imino (-NH-) o metileno (-CH_2-). En todavía otra incorporación X representa imino (-NH-). En una incorporación adicional X representa metileno (-CH_2-).

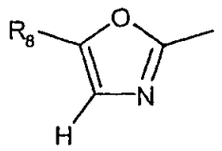
Valores apropiados para el anillo B/sistema de anillo incluyen, por ejemplo, diazepanileno, piperazinileno, piperidinileno, pirrolidinileno y azetidinileno, en donde cualquiera de ellos puede estar presente en cualquiera de sus formas isoméricas (por ejemplo, piperazin- tetrahidropiridazin- tetrahidropirimidina).

Incorporaciones para el anillo B/sistema de anillo incluyen, por ejemplo, diazepanileno, piperazinileno, piperidinileno, pirrolidinileno y

azetidinileno. Otras incorporaciones incluyen estos grupos que se sustituyen con R_{14} que tiene un grupo $(C_1\text{-}C_6)$alquilo, en donde el grupo $(C_1\text{-}C_6)$alquilo se sustituye opcionalmente con un grupo(s) OH, COOH o $COOR^e$, por ejemplo un grupo 2-carboxietilo, y en donde R^e representa arilo, cicloalquilo, heterociclilo o $(C_1\text{-}C_{12})$alquilo sustituido opcionalmente por uno o más de átomos de halógeno (F, Cl, Br, I) o átomos de halógeno mixtos, OH, arilo, cicloalquilo y heterociclilo.

En una alternativa a la incorporación para el anillo B/sistema de anillo anterior, la incorporación incluye, por ejemplo, grupos diazepanileno, piperazinileno, piperidinileno, pirrolidinileno o azetidinileno, que se sustituyen con R_{14} que tiene un grupo $(C_1\text{-}C_6)$alquilo, en donde el grupo $(C_1\text{-}C_6)$alquilo se sustituye opcionalmente con un grupo(s) OH, COOH o $COOR^e$, por ejemplo un grupo 2-carboxietilo, y en donde R^e representa H, arilo, cicloalquilo, heterociclilo o $(C_1\text{-}C_6)$alquilo sustituido opcionalmente por uno o más de átomos de halógeno (F, Cl, Br, I) o átomos de halógeno mixtos, OH, arilo, cicloalquilo y heterociclilo.

Una segunda incorporación de fórmula I se define por;
R_1 representa $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ o un grupo gH,



(gII),

R_2 representa H, CN, NO_2, $(C_1\text{-}C_6)$alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa $(C_1\text{-}C_6)$alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$alquilC(O), $(C_1\text{-}C_6)$alquiltioC(O), $(C_1\text{-}C_6)$alquilC(S), $(C_1\text{-}C_6)$alcoxiC(O), $(C_3\text{-}C_6)$cicloalcoxi, arilo, arilC(O), aril$(C_1\text{-}C_6)$alquilC(O), heterociclilo, heterociclilC(O),

heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(2)}R^{b(2)}$ en la cual $R^{a(3)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Además, R_1 + R_2 juntos (con dos carbonos del anillo piridina) pueden formar una lactona cíclica de 5 ó 6 miembros;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_3 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_3 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(3)}R^{b(3)}$ en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6 alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, COOH, (C_1-C_6)alcoxicarbonilo, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_4 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, 1), OH y/o COOH y/o (C_1-C_3)alcoxicarbonilo; además R_4 representa (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsurfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(4)}R^{b(4)}$ en la cual $R^{a(4)}$ y $R^{b(4)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(4)}$ y $R^{b(4)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Z representa O o está ausente;

R_5 representa H o (C_1-C_6)alquilo;

R_6 representa (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno, (con la salvedad que cualquier oxígeno tal tiene que estar por lo menos 1 átomo de carbono alejado del éster-oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_6 representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_6)alquilo, arilo o heterociclilo;

R_7 representa (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_7 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, arilo o heterociclilo;

R_8 representa H, (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_8 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)Cicloalquil(C_1-C_6)alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo;

R_{14} representa H, OH con la salvedad que el grupo OH tiene que estar por lo menos 2 átomos de carbono alejado de cualquier heteroátomo en el anillo B/sistema de anillo, (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más de OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más de átomos de halógeno (F, Cl, Br, I), OH, arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6) alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)Cicloalquil(C_1-C_6)alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo; o un grupo de fórmula $NR^{a(14)}R^{b(14)}$ en

la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H, OH con la salvedad que el grupo OH tiene que estar por lo menos 2 átomos de carbono alejado de cualquier heteroátomo en el anillo B/sistema de anillo, (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más de OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más de átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{15} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquil(C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil (C_1-C_6) alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6) cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(15)}R^{b(15)}$ en la cual $R^{a(15)}$ y $R^{b(15)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(15)}$ y $R^{b(15)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{16} representa (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_{16} representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, o heterociclilo;

R_{17} representa (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo,

heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_{17} representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{18} representa (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_{18} representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido o polisustituido, un grupo (C_1-C_4)oxoalquileno, un grupo (C_1-C_4)alquilenoxi o un grupo oxi-(C_1-C_4)alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido, (C_1-C_4)alquilenimino o (C_1-C_4)alquilenimino (-N(R_{19})-((C_1-C_4)alquileno) N-sustituido en donde los mencionados grupos alquileno son no sustituidos, o monosustituidos o polisustituidos con cualesquiera sustituyentes de acuerdo con lo anterior; preferiblemente R^c representa imino o (C_1-C_4)alquilenimino o un grupo (C_1-C_4)alquileno o un grupo (C_1-C_4)oxoalquileno no sustituido o monosustituido o polisustituido con cualesquiera sustituyentes de acuerdo con lo anterior;

R_{19} representa H o (C_1-C_4)alquilo;

R^d representa (C_3-C_8)cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos

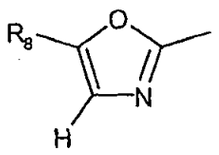
de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, $(C_1$-$C_6)$alquilo, $(C_1$-$C_6)$alcoxiC(O), $(C_1$-$C_6)$alcoxi, $(C_1$-$C_6)$alquilo halógeno sustituido, $(C_3$-$C_6)$cicloalquilo, arilo, heterociclilo, $(C_1$-$C_6)$alquilsulfinil$(C_1$-$C_6)$alquilsulfonilo, $(C_1$-$C_6)$alquiltio, $(C_3$-$C_6)$cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril$(C_1$-$C_6)$alquiltio, aril$(C_1$-$C_6)$alquilsulfinilo, aril$(C_1$-$C_6)$alquilsulfonilo, heterociclil$(C_1$-$C_6)$alquiltio, heterociclil$(C_1$-$C_6)$alquilsulfinilo, heterociclil$(C_1$-$C_6)$alquilsulfonilo, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_6)$alquiltio, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_6)$alquilsulfinilo, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_6)$alquilsulfonilo o un grupo de fórmula $NR^{a(Rd)}R^{b(Rd)}$ en la cual $R^{a(Rd)}$ y $R^{b(Rd)}$ representan independientemente H, $(C_1$-$C_6)$alquilo, $(C_1$-$C_6)$alquilC(O) o $R^{a(Rd)}$ y $R^{b(Rd)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

X representa un enlace simple, imino (-NH-), metileno $(-CH_2-)$, iminometileno $(-CH_2-NH-)$ en donde el carbono se conecta al anillo B/sistema de anillo, metilenimino $(-NH-CH_2-)$ en donde el nitrógeno se conecta al anillo B/sistema de anillo y cualquier carbono y/o nitrógeno en estos grupos puede sustituirse opcionalmente con $(C_1$-$C_6)$ alquilo; además X puede representar un grupo $(-CH_2-)_n$ en donde n= 2-6, que opcionalmente es insaturado y/o se sustituye por uno o más sustituyentes seleccionados entre halógeno, hidroxilo o $(C_1$-$C_6)$alquilo;

B es un anillo/sistema de anillo heterocíclico de 4 a 11 miembros, monocíclico o bicíclico, que comprende uno o más átomos de nitrógeno, opcionalmente uno o más átomos seleccionados de oxígeno o azufre, el cual nitrógeno se conecta al anillo piridina (de acuerdo con fórmula I) y además el anillo B/sistema de anillo se conecta a X en otra de sus posiciones. Los sustituyentes R_{14} y R_{15} se conectan al anillo B/sistema de anillo en tal modo que no se formen compuestos de amonio cuaternario (mediante estas conexiones).

Una tercera incorporación de fórmula I se define por;

R_1 representa $R_6OC(O)$, $R_{16}SC(O)$, o un grupo gII,



(gII),

R_2 representa H, CN, NO_2, (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6) cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O) o un grupo de fórmula $NR^{a(2)}R^{b(2)}$ en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_3 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_3 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_3)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, o un grupo de fórmula $NR^{a(3)}R^{b(3)}$ en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, COOH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_4 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH y/o COOH y/o metoxicarbonilo; además R_4 representa (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O) o un grupo de fórmula $NR^{a(4)}R^{b(4)}$ en la cual $R^{a(4)}$ y $R^{b(4)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(4)}$ y $R^{b(4)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Z representa O ó está ausente;

R_5 representa H o (C_1-C_6)alquilo;

R_6 representa (C_1-C_6)alquilo, interrumpido opcionalmente por oxígeno, (con la salvedad que cualquier oxígeno tal tiene que estar por lo menos 1 átomo de carbono alejado del éster-oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_6 representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_6)alquilo, arilo o heterociclilo;

R_8 representa H, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_8 representa (C_3-C_6)cicloalquilo, hidroxil(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{14} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más de OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquil sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxil(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo o un grupo de fórmula $NR^{a(14)}R^{b(14)}$ en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{15} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo o un grupo de fórmula $NR^{a(15)}R^{b(15)}$ en la cual $R^{a(15)}$ y $R^{b(15)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(15)}$ y $R^{b(15)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{16} es etilo;

R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido o polisustituido, un grupo (C_1-C_4)oxoalquileno, un grupo

$(C_1$-$C_4)$alquilenoxi o un grupo oxi-$(C_1$-$C_4)$alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de $(C_1$-$C_4)$alquilo, $(C_1$-$C_4)$alcoxilo, oxi-$(C_1$-$C_4)$alquilo, $(C_2$-$C_4)$alquenilo, $(C_2$-$C_4)$alquinilo, $(C_3$-$C_6)$cicloalquilo, carboxilo, carboxi-$(C_1$-$C_4)$alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, $(C_1$-$C_4)$alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido, $(C_1$-$C_4)$alquilenimino o $(C_1$-$C_4)$alquilenimino (-$N(R_{19})$-($(C_1$-$C_4)$alquileno) N-sustituido, en donde los mencionados grupos alquileno son no sustituidos, o monosustituidos o polisustituidos con cualesquiera sustituyentes de acuerdo con lo anterior; preferiblemente R^c representa imino o $(C_1$-$C_4)$alquilenimino o un grupo $(C_1$-$C_4)$alquileno o un grupo $(C_1$-$C_4)$oxoalquileno no sustituido o monosustituido o polisustituido con cualesquiera sustituyentes de acuerdo con lo anterior;

R_{19} representa H o $(C_1$-$C_4)$alquilo;

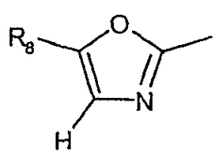
R^d representa $(C_3$-$C_8)$cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, CN, NO_2, $(C_1$-$C_6)$alquilo, $(C_1$-$C_6)$alcoxi, $(C_1$-$C_6)$alquilo halosustituido, $(C_3$-$C_6)$cicloalquilo, arilo, heterociclilo, $(C_1$-$C_6)$alquilsulfinilo, $(C_1$-$C_6)$alquilsulfonilo, $(C_1$-$C_6)$alquiltio, $(C_3$-$C_6)$cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril$(C_1$-$C_6)$alquiltio, aril$(C_1$-$C_6)$alquilsulfinilo, aril$(C_1$-$C_6)$alquilsulfonilo, heterociclil$(C_1$-$C_6)$alquiltio, heterociclil$(C_1$-$C_6)$alquilsulfinilo, heterociclil$(C_1$-$C_6)$alquilsulfonilo, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_6)$alquiltio, $(C_3$-$C_6)$cicloalquil$(C_1$-$C_6)$alquilsulfinilo o $(C_3$-$C_6)$cicloalquil$(C_1$-$C_6)$alquilsulfonilo;

X representa un enlace simple, imino (-NH-), metileno (-CH_2-), iminometileno (-CH_2-NH-) en donde el carbono se conecta al anillo B/sistema de anillo, metilenimino (-NH-CH_2-) en donde el nitrógeno se conecta al anillo B/sistema de anillo y cualquier carbono y/o nitrógeno en estos grupos puede sustituirse opcionalmente con (C_1-C_6) alquilo; además X puede representar un grupo (-CH_2-)$_n$ en donde n= 2-6, que opcionalmente es insaturado y/o se sustituye por uno o más sustituyentes seleccionados entre halógeno, hidroxilo o (C_1-C_6)alquilo;

B es un anillo/sistema de anillo heterocíclico de 4 a 11 miembros, monocíclico o bicíclico, que comprende uno o más átomos de nitrógeno y opcionalmente uno o más átomos seleccionados de oxígeno o azufre, el cual nitrógeno se conecta al anillo piridina (de acuerdo con fórmula I) y además el anillo B/sistema de anillo se conecta a X en otra de sus posiciones. Los sustituyentes R_{14} y R_{15} se conectan al anillo B/sistema de anillo en tal modo que no se formen compuestos de amonio cuaternario (mediante estas conexiones).

Una cuarta incorporación de fórmula I se define por;

R_1 representa $R_6OC(O)$, $R_{16}SC(O)$ o un grupo gII



(gII),

R_2 representa H o interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa un grupo de fórmula $NR^{a(2)}R^{b(2)}$ en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_3 representa H o un grupo de fórmula $NR^{a(3)}R^{b(3)}$ en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa CN, halógeno (F, Cl, Br, I), además R_4 representa (C_1-C_6)alquilC(O), (C_1-C_6)alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH y/o COOH y/o metoxicarbonilo;

Z representa O o está ausente;

R_5 representa H;

R_6 representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno, (con la condición que cualquier oxígeno similar tiene que estar alejado por lo menos 2 átomos de carbono del éster-oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_6 representa (C_3-C_6)cicloalquilo o hidroxi(C_2-C_{12})alquilo;

R_8 representa H, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I);

R_{14} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa un

grupo de fórmula $NR^{a(14)}R^{b(14)}$ en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, $(C_1$-$C_6)$alquilo, $(C_1$-$C_6)$alquilC(O), $(C_1$-$C_6)$alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H;

R_{16} es etilo;

R^c representa un grupo $(C_1$-$C_4)$alquilenono sustituido o monosustituido, un grupo $(C_1$-$C_4)$alquilenoxi o un grupo oxi-$(C_1$-$C_4)$alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de $(C_1$-$C_4)$alquilo; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido;

R_{19} representa H o metilo;

R^d representa $(C_3$-$C_8)$cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, CN, NO_2, $(C_1$-$C_6)$alquilo, $(C_1$-$C_6)$alcoxi, $(C_1$-$C_6)$alquilo halosustituido;

X representa un enlace simple, imino (-NH-) o metileno (-CH_2-); y

B es una anillo/sistema de anillo heterocíclico de 4 a 11 miembros, monocíclico o bicíclico, que comprende uno o más nitrógeno y opcionalmente uno o más átomos seleccionados de oxígeno y azufre, el cual nitrógeno se conecta al anillo piridina (de acuerdo con la fórmula I) y, además, el sistema de anillo/anillo B se conecta a X en otra de sus posiciones. Los sustituyentes R_{14} y R_{15} se conectan al sistema de anillo/anillo B, en tal manera que no se formen compuestos de amonio cuaternario (mediante estas conexiones).

Una quinta incorporación de fórmula I se define por el hecho que:

R_1 se selecciona de un grupo conformado por metoxicarbonilo, etoxicarbonilo, (n-propil)-oxicarbonilo, (iso-propil)-oxicarbonilo, (iso-butil)-oxicarbonilo, (*terc*-butil)-oxicarbonilo, (2,2-dimetil-propil)-oxicarbonilo, (ciclo-propil)-oxicarbonilo, (ciclo-butil)-oxicarbonilo, (ciclo-pentil)-oxicarbonilo, (2-hidroxietil)-oxicarbonilo), (2,2,2- trifluoroetil)-oxicarbonilo, bencil-oxicarbonilo, 4-fluorobencil-oxicarbonilo, etiltiocarbonilo, y 5-etil-1,3-oxazol-2-ilo;

R_2 se selecciona de un grupo conformado por H, metilo, etilo, isopropilo, y dimetilamino;

R_3 se selecciona de un grupo conformado por H y amino;

R_4 se selecciona de un grupo conformado por metoxi, cloro, ciano, (4-metoxi-4-oxobutoxi), (3-carboxi-propoxi) y metilcarbonilo;

Z representa O o está ausente;

R_5 es H;

R_6 se selecciona de un grupo conformado por metilo, etilo, 2-hidroxietilo, (2,2,2-trifluoroetilo), n-propilo, iso-propilo, ciclo-propilo, iso-butilo, *terc*-butilo, ciclo-butilo, 2,2-dimetilpropilo, ciclo-pentilo, bencilo y 4-fluorobencilo;

R_8 es etilo;

R_{14} se selecciona de un grupo conformado por H, metilo, *terc*-butiloxicarbonil-imino y amino;

R_{15} es H;

R_{16} es etilo;

R^c se selecciona de un grupo conformado por metileno ($-CH_2-$), metilmetileno (-CH(CH3)-), etileno ($-CH_2CH_2-$), oxipropileno ($-OCH_2CH_2CH_2-$), imino (-NH-) y metilimino ($-N(CH_3)-$;

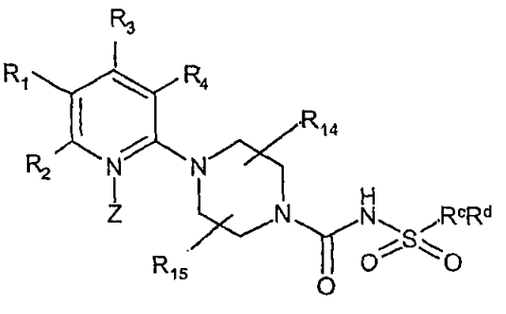
R_{19} se selecciona de un grupo conformado por H y metilo;

R^d se selecciona de un grupo conformado por ciclopentilo, ciclohexilo, 4-metilciclohexilo, fenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 4-etilfenilo, 2-metoxicarbonil-fenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, 2-(trifluorometil)fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 3- clorofenilo, 4-clorofenilo, 3-bromofenilo, 4-cianofenilo, 4-metoxifenilo, 2-nitrofenilo, 3-nitrofenilo, 4-nitrofenilo, 3,4-diclorofenilo, 3,5-diclorofenilo, 3,4-difluorofenilo, 2,5-dimetilfenilo, 3,5-dimetilfenilo, 4-isopropilfenilo, 3-fluoro-4-metil-fenilo, 2-piridilo, 3-piridilo, 4-piridilo, N-óxido-2-piridilo, 6-[3-benzo[d]isoxazol-3-ilo] y N-[(1,2-benzisoxazol-3-ilo)];

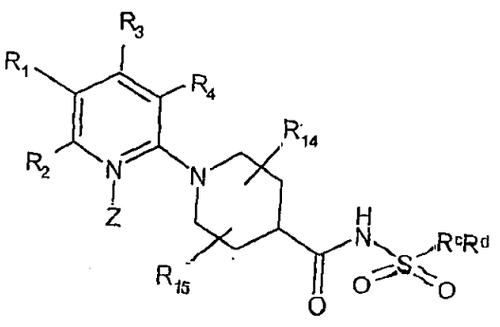
X representa un enlace simple, imino (-NH-) o metileno (-CH_2-);

B se selecciona del grupo conformado por 4-piperazin-1-ileno, 4-piperidin-1-ileno, 3-piperidin-1-ileno, 3-azetidin-1-ileno, y los sustituyentes R_{14} y R_{15} se conectan al sistema de anillo/anillo B, en tal manera que no se formen compuestos de amonio cuaternario (mediante estas conexiones).

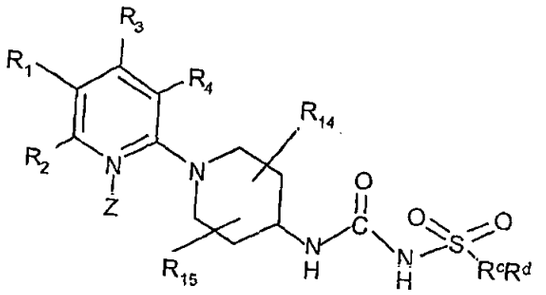
En una sexta incorporación de fórmula (I), fórmula (I) se define como siendo cualquier compuesto(s) de fórmula (Ia)-(Ii):



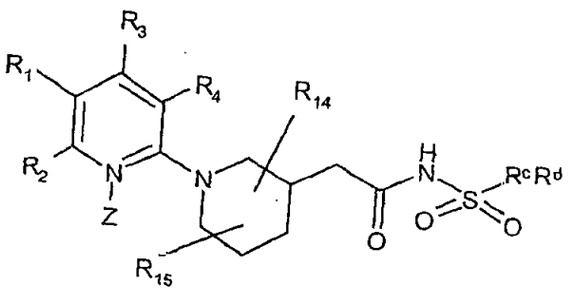
(Ia)



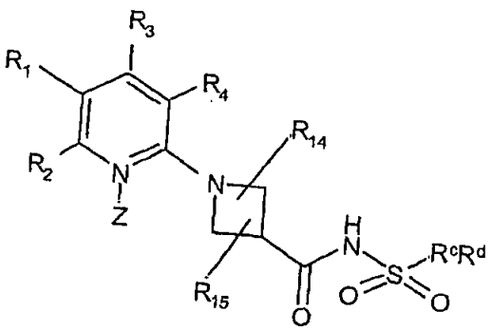
(Ib)



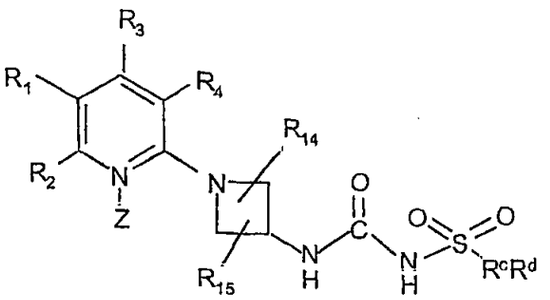
(Ic)



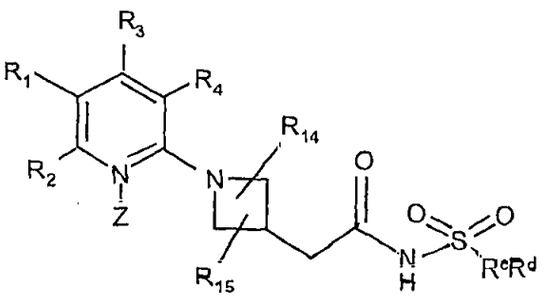
(Id)



(Ie)



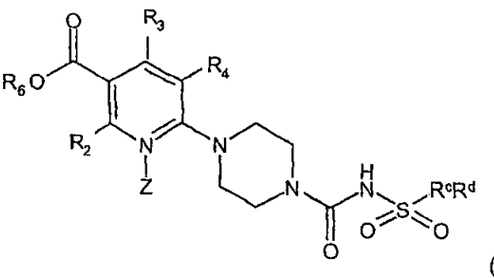
(If)



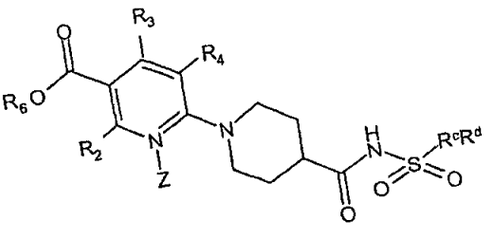
(Ig).

En las anteriores fórmulas Ia - Ig los diferentes valores de Z y R (excepto R_5 que es H) son como ya se definieron e incluyen las incorporaciones mencionadas previamente.

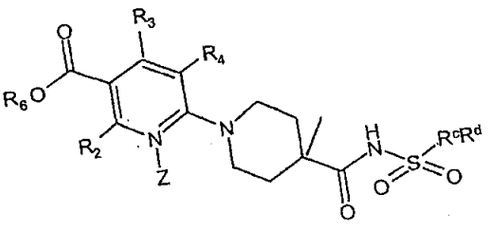
En una séptima incorporación, fórmula (I) se define como siendo cualquier compuesto(s) de fórmula (Iaa)-(Ijj);



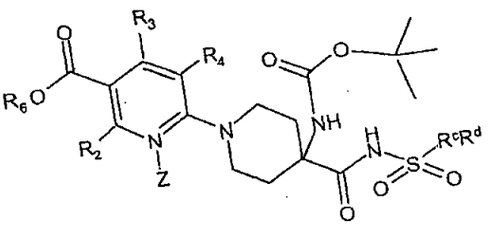
(Iaa)



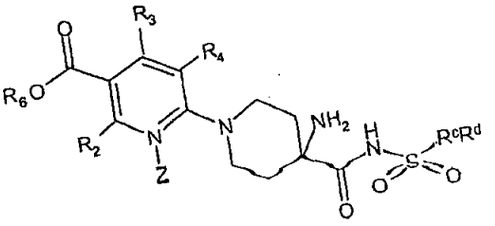
(Ibb)



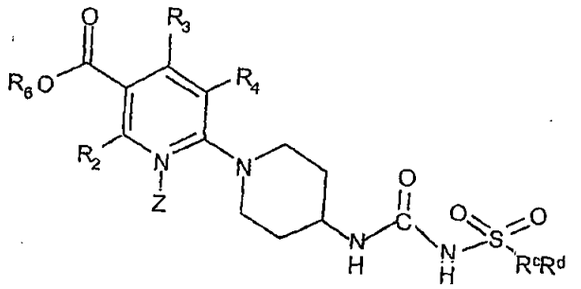
(Ibc)



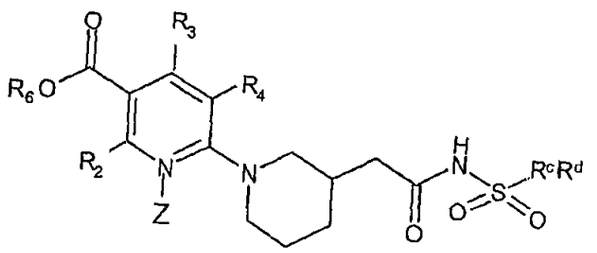
(Ibd)



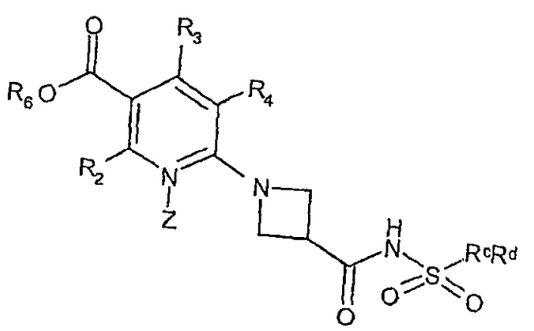
(Ibe)



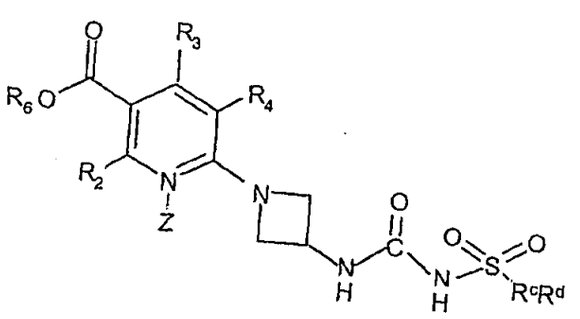
(Icc)



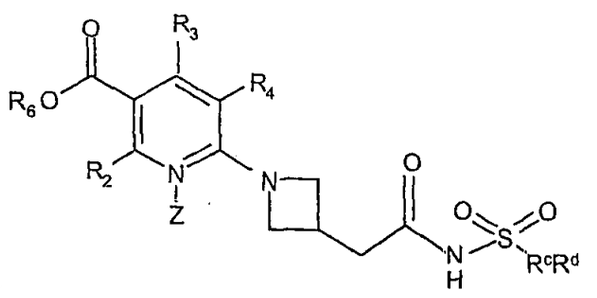
(Idd)



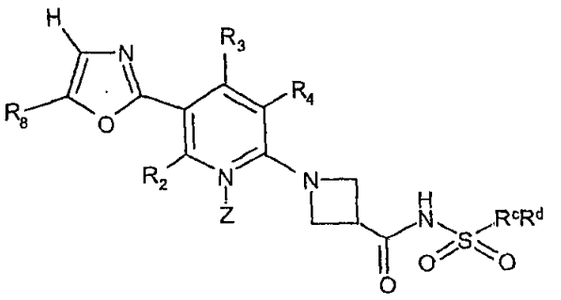
(Iee)



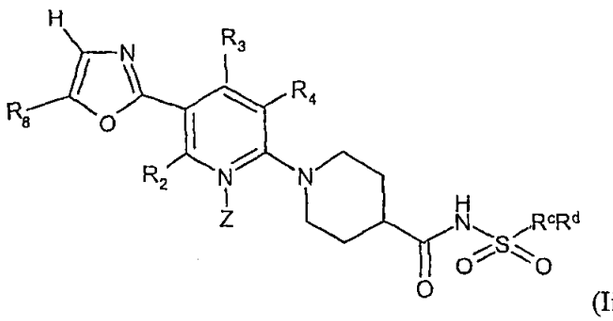
(Iff)



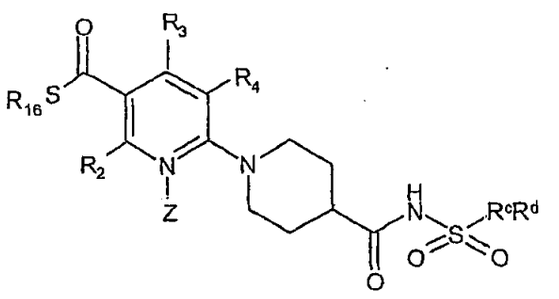
(Igg)



(Ihh)



(Iii).



(Ijj).

En las fórmulas anteriores Iaa - Ijj los diferentes valores de Z y R (excepto R_5, R_{14} y R_{15}, todos los cuales son H) son como ya se definió e incluyen las incorporaciones mencionadas previamente.

Ejemplos de compuestos específicos de acuerdo con la invención pueden seleccionarse de:

etil éster de ácido 5-ciano-6-[3-(1-metoxicarbonil-fenilmetanosulfonilaminocarbonil)- azetidin-1-il]-2-metil-nicotínico;

etil éster de ácido 6-[3-({[(3-bromobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-metilnicotínico;

etil éster de ácido 5-ciano-2-metil-6-[3-(2-nitro-fenilmetanosulfonilaminocarbonil)-zetidin-1-il]- nicotínico;

etil éster de ácido 6-[3-(2-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;
etil éster de ácido 6-[3-(4-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(4-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-6-[3-(3-fluoro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(3-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 6-[3-(3-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;
etil éster de ácido 6-{3-[2-(3-cloro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-5-ciano-2-metil-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(4-nitro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(2-fenil-etanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-(3-o-tolilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(3-nitro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-6-{3-[2-(4-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(2-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-6-[3-(4-fluoro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-(3-ciclopentilmetanosulfonilaminocarbonil-azetidin-1-il)-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-{3-[2-(2-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico;

etil éster de ácido 5-ciano-6-[3-(3,5-dicloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-(3-ciclohexilmetanosulfonilaminocarbonil-azetidin-1-il)-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-{3-[2-(3-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin- 1-il}-2-metil-nicotínico;
etil éster de ácido 6-[3-(benzo[d]isoxazol-3-ilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;
1-[4-amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]-*N*-(bencilsulfonil)piperidin-4-carboxamida;
etil éster de ácido 4-amino-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloronicotínico;
isopopil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicotínico;
terc-butil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicotínico;
etil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino)azetidin-1-il]-5-ciano-2-metilnicotínico;
etil éster de ácido 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}piperidin-1-il)-5-ciano-2-metilnicotínico;
etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}-4-metilpiperidin-1-il)-5-ciano-2-metilnicotínico;
N-(bencilsulfonil)-1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxamida;
Ciclopentil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico;
propil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico;
etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-isopropilnicotínico;
etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-etilnicotínico;

2,2-dimetilpropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico;
N-(bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida;
isopropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico;
isopropil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico;
etil éster de ácido 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotínico;
etil éster de ácido 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotínico;
etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico;
N-[(1,2-benzisoxazol-3-ilmetil)sulfonil]-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida;
N-(bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]azetidin-3-carboxamida;
N-[(4-clorobencil)sulfonil]-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida;
etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico;
etil 5-ciano-6-{3-[({[3-(4-metoxifenoxi)propil]sulfonil}amino) carbonil] azetidin-1-il}-2-metilnicotinato;
etil 4-amino-6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloronicotinato;
etil 5-ciano-2-metil-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;
2,2-dimetilpropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;
etil 5-ciano-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 6-[4-({[(3-bromobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato;

ciclopropil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

2,2,2-trifluoroetil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)- 5-ciano-2-metilnicotinato;

2,2,2-trifluoroetil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)- 5-ciano-2-metilnicotinato;

2,2,2-trifluoroetil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-metilnicotinato;

ciclopropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

ciclobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

2-hidroxietil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

bencil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino} carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(3,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino} carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-isopropilnicotinato;

etil 6-(3-{[bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-etilnicotinato;

etil 5-ciano-2-metil-6-[3-({[(1-feniletil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato;

propil 6-(3-{[(bencilsulfonil)amino]carbonil)azetidin-1-il)-5-ciano-2-metilnicotinato;

isobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

isopropil 5-ciano-2-metil-6-{4-[({[4-(trifluorometil)bencil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato;

isopropil 5-ciano-2-metil- 6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

isopropil 5-ciano-2-metil-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

isopropil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato;

isopropil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il] -5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-6-{4-[({[2-(metoxicarbonil)bencil]sulfonil}amino)carbonil] piperidin-1-il}-2-metilnicotinato;

etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-2-metil-6-{4-[({[2-(2-metilfenil)etil] sulfonil}amino) carbonil] piperidin-1-il}nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato;

ácido 4-{[2-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato;

etil 6-(4-{[(anilinosulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-{4-[({[metil(fenil)amino]sulfonil}amino)carbonil] piperidin-1-il}nicotinato;

isopropil 5-ciano-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

isopropil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-2-metil-6-[3-({[(2-feniletil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

isopropil 5-ciano-6-[3-({[(ciclopentilmetil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-{3-[({[2-(metoxicarbonil)bencil]sulfonil}amino) carbonil]azetidin-1-il}-2-metilnicotinato;

isopropil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]- 5-ciano-2-metilnicotinato;

isopropil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

metil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

metil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

S-etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilpiridin-3-carbotioato;

S-etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil) piperidin-1-il]piridin-3-carbotioato;

S-etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilpiridin-3-carbotioato;

S-etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilpiridin-3-carbotioato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-metoxi-2-metilnicotinato;

etil 6-[4-({[(bencilsulfonil)amino]carbonil}amino)piperidin-1-il]-5-ciano-2-metilnicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperazin-1-il)-5-ciano-2-metilnicotinato;

ácido 4-{[2-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico;

etil 5-ciano-2-metil-6-{3-[({[(1-oxidopiridin-2-il)metil]sulfonil}amino) carbonil]azetidin-1-il}nicotinato;

etil 5-ciano-2-metil-6-[3-({[(piridin-3-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-{4-[({[(1-oxidopiridin-2-il)metil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato;

etil 5-ciano-2-metil-6-[4-({[(piridin-3-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(dimetilamino)nicotinato;

etil 5-ciano-2-metil-6-[4-({[(piridin-4-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-[3-({[(piridin-2-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(3,5-dimetilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(2,5-dimetilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(4-isopropilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

bencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-{4-[({[(4-metilciclohexil)metil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato;

etil 5-ciano-6-[3-({[(4-isopropilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-2-metil-6-[4-({[(2-feniletil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-[4-({[(piridin-2-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(2,5-dimetilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloro-2-metilnicotinato;

etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-(2-{[(4-fluorobencil)sulfonil]amino}-2-oxoetil) azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(3-fluoro-4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-metilnicotinato;

4-fluorobencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-6-[4-({[(4-etilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(3,4-difluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(4-metoxibencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-2-metil-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(4-etilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

etil 5-cloro-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-6-[4-({[(3,4-difluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(4-metoxibencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

ciclopropil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-[3-({[(piridin-4-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(dimetilamino)nicotinato;

1-óxido de etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-acetil-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-2-metilnicotinato;

etil 6-{4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil)amino] piperidin-1-il}-5-ciano-2-metilnicotinato;

etil 6-(4-amino-4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-(difluorometil)nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(difluorometil)nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(trifluorometil)nicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(trifluorometil)nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(fluorometil)nicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(fluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-{4-[({[(4-metilciclohexil)metil]sulfonil}amino)carbonil]piperidin-1-il}nicotinato;

etil 5-ciano-2-(difluorometil)-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato;

etil 5-ciano-2-(difluorometil)-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato;

etil 5-ciano-2-(difluorometil)-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato;

etil 5-ciano-2-(difluorometil)- 6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato;

etil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato;

etil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato;

etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato;

etil 5-ciano-2-(difluorometil)-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato;

etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)- 6-[3-({[(3-fluorobencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato;

etil 5-ciano-2-(difluorometil)-6-[3-({[(4-fluorobencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato;

etil 6-[3-({[(2-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato;

etil 6-[3-({[(3-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato;

etil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-[3-({[(3-metilbencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato;

etil 5-ciano-2-(difluorometil)-6-[3-({[(4-metilbencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometilmetilciclohexil)metil]sulfonil}amino)carbonil] azetidin-1-il}nicotinato;

etil 5-ciano-6-[3-({[(3-cianofenil)sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-6-[3-({[(4-cianofenil)sulfonil]amino}carbonil)azetidin-1 -il]-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-{3-[({[4-(trifluorometoxi)fenil]sulfonil} amino)carbonil]azetidin-1-il}nicotinato;

etil 5-ciano-2-(difluorometil)-6-{3-[({[2-(trifluorometoxi)fenil]sulfonil} amino) carbonil]azetidin-1-il}nicotinato;

etil 5-ciano-6-[3-({[(2-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-(3-{[(2-naftilsulfonil)amino]carbonil} azetidin-1-il)nicotinato;

etil 6-(3-{[(butilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato;

etil 5-ciano-6-[4-({[(3-cianofenil)sulfonil]amino}carbonil)piperidin-1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-6-[4-({[(4-cianofenil)sulfonil]amino}carbonil)piperidin- 1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-{4-[({[4-(trifluorometoxi)fenil]sulfonil} amino)carbonil]piperidin-1-il}nicotinato;

etil 5-ciano-2-(difluorometil)-6-{4-[({[2-(trifluorometoxi)fenil]sulfonil} amino)carbonil]piperidin-1-il}nicotinato;

etil 5-ciano-6-[4-({[(2-cianobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(difluorometil)nicotinato;

etil 5-ciano-2-(difluorometil)-6-(4-{[(2-naftilsulfonil)amino]carbonil} piperidin-1-il)nicotinato;

etil 6-(4-{[(butilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(difluorometil)nicotinato;

etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}pirrolidin-1-il)-5-ciano-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-(2-oxo-2-{[(2-feniletil)sulfonil]amino}etil)pirrolidin-1-il]-2-(trifluorometil)nicotinato;

etil 6-[3-(2-{[(5-cloro-2-tienil)sulfonil]amino}-2-oxoetil)pirrolidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1 -il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil)azetidin- 1-il]-2-(trifluorometil)nicotinato;

etil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 6-[3-({[(2-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 6-[3-({[(3-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato;

etil 6-[3-({[(5-cloro-2-tienil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato;

etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(trifluorometil)nicotinato;

etil 6-[4-({[(5-cloro-2-tienil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato;

etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil)nicotinato;

etil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil)nicotinato;

etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil)nicotinato;

etil 6-[3-({[(2-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato;

etil 6-[3-({[(3-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato;

etil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato;

etil 5-ciano-2-(fluorometil)-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-2-(fluorometil)-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(fluorometil)nicotinato;

etil 5-ciano-2-(fluorometil)-6-{3-[({[(4-metilciclohexil)metil]sulfonil} amino) carbonil]azetidin-1-il}nicotinato;

etil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil)nicotinato;

etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil)nicotinato;

etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil)nicotinato;

etil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato;

etil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato;

etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato;

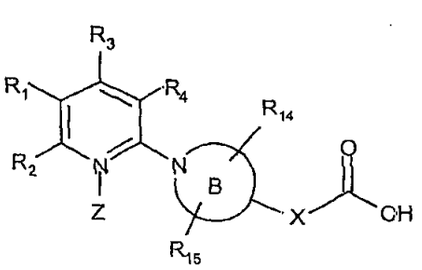
etil 5-ciano-2-(fluorometil)-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;
etil 5-ciano-2-(fluorometil)-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;
etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(fluorometil)nicotinato;
etil 5-ciano-2-(fluorometil)-6-{4-[({[(4-metilciclohexil)metil]sulfonil} amino) carbonil]piperidin-1-il}nicotinato;
etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato;
y sus sales farmacéuticamente aceptables.

Procesos

Los siguientes procesos, junto con los intermedios, se proveen como una característica adicional de la presente invención.

Compuestos de fórmula (I) pueden prepararse por los siguientes procesos *a1-a8*;

a1) Compuestos de fórmula (I) en la cual R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z, R^c y R^d se definen como anteriormente, X es un enlace simple o un carbono, pueden formarse haciendo reaccionar un compuesto de fórmula (II), en la cual R_1, R_2, R_3, R_4, B, Z, R_{14} y R_{15} se definen



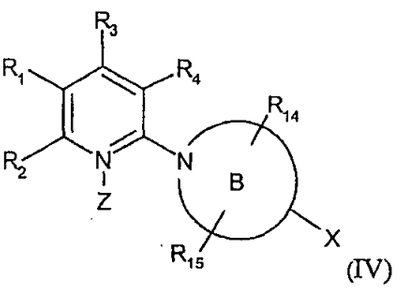
(II)

como anteriormente, X es un enlace simple o un carbono, con un compuesto de fórmula (III) en la cual R_5, R^c y R^d se definen como anteriormente.

$$R_5\text{-}NHSO_2\text{-}R^c\text{-}R^d \qquad \text{(III)}$$

La reacción se lleva generalmente a cabo en un disolvente orgánico inerte tal como diclorometano a temperatura ambiente. La reacción puede realizarse empleando condiciones estándar o en la presencia de EDCI y HOBT. Opcionalmente, la reacción puede efectuarse en la presencia de una base orgánica tal como trietilamina o DIPEA.

a2) Compuestos de fórmula (I) en la cual R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z, R^c y R^d se definen como anteriormente, X es un nitrógeno o un enlace simple conectado a un nitrógeno que es un miembro del anillo B, pueden formarse haciendo reaccionar un compuesto de fórmula (IV), en la cual R_1, R_2, R_3, R_4, R_{14}, y R_{15} se definen como anteriormente y X es un nitrógeno o un hidrógeno, con un compuesto de la



(IV)

fórmula general (III), como se define más arriba.
La reacción se lleva generalmente a cabo en un disolvente inerte tal como DCM. La reacción puede realizarse en la presencia de CDI. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica apropiada tal como trietilamina o DIPEA.

a3) Compuestos de fórmula (I) en la cual R_1, R_2, R_3, R_4, B, R_{14}, R_{15}, Z, R^c y R^d se definen como anteriormente, R_5 es un hidrógeno, X es un nitrógeno o un enlace simple conectado a un nitrógeno que es un miembro del anillo B, pueden formarse haciendo reaccionar un compuesto de fórmula (IV) que se define en *a2*) de más arriba, con un compuesto de fórmula (V)

$$O= C= N\text{-}SO_2\text{-}\ R^cR^d \quad (V)$$

en la cual R^c y R^d son como se define anteriormente.

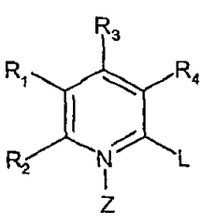
La reacción se lleva generalmente a cabo en un disolvente inerte tal como THF. La reacción puede realizarse igualmente en la presencia de una base orgánica tal como trietilamina o DIPEA.

a4) Compuestos de fórmula (I) en la cual R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z, R^c y R^d se definen como anteriormente, X es un nitrógeno o un enlace simple conectado a un nitrógeno que es un miembro del anillo B, pueden formarse haciendo reaccionar un compuesto de fórmula (IV) que se define más arriba, con un compuesto de fórmula (VI),

$$R^dR^c\text{-}SO_2NR_5\text{-}COOCH_2CCl_3 \qquad (VI)$$

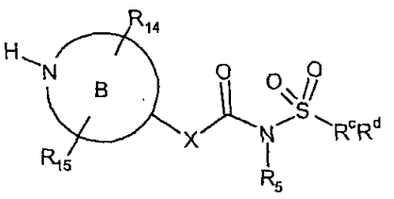
en la cual R_5, R^c y R^d son como se definen anteriormente. La reacción se lleva generalmente a cabo en un disolvente tal como DMA. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como trietilamina o DIPEA.

a5) Compuestos de fórmula (I) pueden prepararse asimismo haciendo reaccionar un compuesto de fórmula (VII) en la cual R_1, R_2, R_3, R_4 y Z se definen como anteriormente y L es un grupo saliente apropiado, tal como cloro, bromo, yodo, triflato o tosilo,



(VII)

con un compuesto de la fórmula general (VIII) en la cual B, R_5, R_{14}, R_{15}, R^c y R^d se definen como en fórmula (I).



(VIII)

La reacción se lleva generalmente a cabo en un disolvente tal como DMA. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como trietilamina o DIPEA.

La reacción se lleva generalmente a cabo a temperaturas elevadas empleando equipo estándar o en un horno microondas de nodo simple.

Generalmente, utilizar el ión híbrido (***"zwitterion"***) de (VIII) cuando R_5 es H, lleva a tiempos de reacción más cortos que cuando se emplea la sal correspondiente de la amina de anillo B, por ejemplo la sal HCl.

Para algunos compuestos, es ventajoso llevar a cabo la reacción en etanol en la presencia de una base orgánica tal como trietilamina.

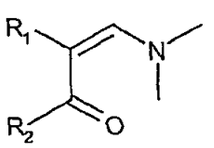
a6) Compuestos de fórmula (I) donde R_1 representa $R_6OC(O)$ y R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, X, Z, R^c y R^d se definen como para fórmula (I), pueden transesterificarse usando procedimientos estándar o haciendo reaccionar con un reactivo $R_{6'}\text{-}O^-L_1^+$, para convertirse en otro compuesto de la fórmula general (I) en donde R_1 se vuelve $R_{6'}OC(O)$.

a7) Un compuesto de fórmula (I) en la cual R_1, R_2, R_3, R_4, B, R_5, R_{15}, R_{15}, Z y R^d son como ya se definieron y R^c representa imino (-NH-) o (C_1-C_4)alquilimino, en el cual el grupo imino podría sustituirse usando condiciones estándar o empleando un agente alquilante como $L\text{-}R_{19}$, en la cual R_{19} es como ya se definió y L es un grupo saliente ejemplificado por cloro, bromo, yodo, triflato o tosilo, para producir compuestos de fórmula (I) en la cual R_1, R_2, R_3, R_4, B, R_5, R_{14}, R_{15}, Z y R^d son como ya se

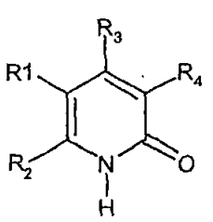
definieron y R^c representa imino (-NR_{19}-) N-sustituido o (C_1-C_4)alquilimino (-N(R_{19})-((C_1-C_4)alquilo) N-sustituido, opcionalmente en la presencia de una base fuerte tal como NaH.

a8) Ciertos compuestos de fórmula (I) en la cual R_2, R_3, R_4, B, R_{14}, R_{15}, R^c y R^d son como ya se definieron, R_1 es $R_6OC(O)$ en donde R_6 es como ya se definió, X es un enlace simple, Z está ausente y R_5 es hidrógeno, se preparan ventajosamente por los siguientes pasos (a8:1 - a8:5);

a8:1) Hacer reaccionar un compuesto de la fórmula $R_1CH_2C(O)R_2$, con dimetoxi-N,N-dimetilmetanoamina para formar un compuesto de la fórmula



a8:2) Este compuesto se hace reaccionar posteriormente con un compuesto de la fórmula general $R_4CH_2C(O)NH_2$, en la cual R_4 se define como para fórmula (I) para producir un compuesto de la fórmula general



, en la cual R_2, R_3, R_4 son como se definen más arriba para fórmula (I), R_1 es $E_6OC(O)$, en donde R_6 es como ya se definió y Z está ausente. La reacción se lleva generalmente a cabo en un disolvente inerte tal como etanol. Esta reacción se realiza en la presencia de una base fuerte tal como etóxido de sodio. El proceso se efectúa posteriormente en forma ventajosa lavando el producto final con una solución de agua alcalina, por ejemplo, una solución de bicarbonato de sodio.

a8:3) El compuesto de *a8:2*) se hace reaccionar con un agente clorante tal como cloruro de tienilo para producir un compuesto de fórmula

(VH) en donde L es cloro. Una mejora adicional de esta reacción es agregar dimetilformamida. Ventajosamente, la reacción se lleva a cabo en un disolvente inerte tal como tolueno.

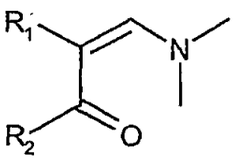
a8:4) Compuestos de la fórmula general (VIII) en la cual B, R_{14}, R_{15}, R^c y R^d son como ya se definieron, X es un enlace simple y R_5 es un hidrógeno, se forman haciendo reaccionar un compuesto de fórmula (X) con un compuesto de fórmula (III), en la cual se protege el nitrógeno del anillo, por ejemplo con t-butiloxicarbonilo. La reacción se lleva generalmente a cabo en un disolvente orgánico inerte tal como THF. La reacción se efectúa usando un reactivo de acoplamiento tal como TBTU. Opcionalmente, la reacción se efectúa en la presencia de una base orgánica tal como trietilamina o DIPEA. Una mejora adicional de esta reacción es agregar LiCl. Cuando el producto contiene un t-butiloxicarbonilo, este grupo se retira empleando procedimientos estándar o en la presencia de ácido fórmico. En una incorporación ventajosa del proceso (*a8*), el producto se aisla como un ión híbrido ajustando el pH de la mezcla de reacción a entre aproximadamente 5-9 con amoníaco disuelto en agua.

a8:5) El producto de *a8:3* se hace reaccionar con el producto de *a8:4*, preferencialmente el ión híbrido, para producir un compuesto de fórmula (I) en la cual R_2, R_3, R_4, B, R_{14}, R_{15}, R^c y R^d son como ya se definieron, R_1 es $R_6OC(O)$ en donde R_6 es como ya se definió, X es un enlace simple, Z está ausente y R_5 es hidrógeno. La reacción se lleva generalmente a cabo en un disolvente inerte tal como etanol a temperaturas elevadas. Opcionalmente, la reacción se efectúa en la presencia de una base orgánica tal como trietilamina. En una incorporación ventajosa del proceso (*a8*) el producto final se purifica y se aisla por recristalización de acetato de etilo.

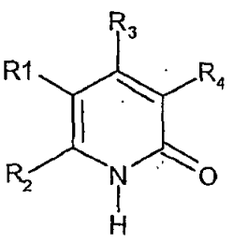
En consecuencia, en una incorporación de la invención, un proceso ventajoso para fabricar un compuesto de fórmula (I) en la cual R_2, R_3, R_4, R_6, B, R_{14}, R_{15}, R^c y R^d se definen de acuerdo con lo anterior, R_1 es $R_6OC(O)$ en donde R_6 es como ya se definió, X es un enlace simple, Z está

ausente y R_5 es hidrógeno, se caracteriza por que el proceso comprende los siguientes pasos (i-vi):

i.) Hacer reaccionar un compuesto de la fórmula $R_1CH_2C(O)R_2$, con dimetoxi-N,N-dimetilmetanoamina para formar un compuesto de la fórmula



ii.) Hacer reaccionar el compuesto del paso i.) con un compuesto de la fórmula general $R_4CH_2C(O)NH_2$ en un disolvente inerte tal como etanol en la presencia de una base fuerte tal como etóxido de sodio, para producir un compuesto de la fórmula general



en la cual R_2, R_3, R_4, se definen de acuerdo con lo anterior, R_1 es $R_6OC(O)$ en donde R_6 se define de acuerdo con lo anterior, y Z está ausente.

iii) El producto del paso ii) se lava primero con una solución de agua alcalina, por ejemplo, una solución de bicarbonato de sodio y luego se lava con agua, después de lo cual el producto lavado se recoge.

iv.) El compuesto del paso iii) se hace reaccionar con un agente clorante tal como cloruro de tionilo en un disolvente inerte, para producir un compuesto de fórmula (VII) en donde L es cloro.

v.) Hacer reaccionar un compuesto de fórmula (X) con un compuesto de fórmula (III), en la cual B, R_{14}, R_{15}, R^c y R^d se definen de acuerdo con lo anterior, X es un enlace simple y R_5 es hidrógeno, mientras el compuesto de fórmula (III) tiene protegido el nitrógeno del anillo con t-butiloxicarbonilo,

en un disolvente orgánico inerte, en la presencia de un reactivo de acoplamiento y opcionalmente una base orgánica tal como trietilamina o DIPEA, para producir un compuesto de la fórmula general (VIII), luego de la desprotección estándar del t-butiloxicarbonilo.

vi) El producto del paso v.) se hace reaccionar con el producto del paso iv.) en un disolvente inerte, opcionalmente en la presencia de una base orgánica tal como trietilamina, para producir un compuesto de fórmula (I) en la cual R_2, R_3, R_4, B, R_{14}, R_{15}, R^c y R^d se definen de acuerdo con lo anterior, R_1 es $R_6OC(O)$ y R_5 se define de acuerdo con lo anterior, X es un enlace simple, Z está ausente y R_5 es hidrógeno.

En una incorporación separada del proceso el paso iv.) comprende agregar dimetilformamida a la mezcla de reacción.

En otra incorporación separada del proceso ventajoso, el paso iv.) comprende agregar dimetilformamida a la mezcla de reacción, y el disolvente inerte en el paso iv.) es tolueno.

En otra incorporación separada del proceso ventajoso, es posible combinar una o más de las incorporaciones del proceso anterior seleccionando que el disolvente orgánico en el paso v.) sea THF.

En una incorporación separada adicional del proceso, es posible combinar una o más de las incorporaciones del proceso anterior seleccionando que el reactivo de acoplamiento en el paso v.) sea TBTU.

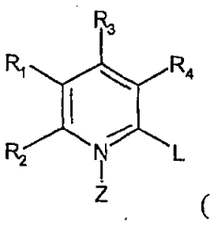
En una incorporación separada adicional del proceso ventajoso, es posible combinar una o más de las incorporaciones del proceso anterior agregando LiCl a la mezcla de reacción en el paso v.).

En todavía una incorporación separada adicional del proceso ventajoso, posible combinar una o más de las incorporaciones del proceso previo aislando el producto obtenido en el paso v.) agregando amoníaco disuelto en agua.

En todavía una incorporación separada adicional del proceso ventajoso, posible combinar una o más de las incorporaciones del proceso previo purificando y aislando el producto del paso vi) mediante recristalización de acetato de etilo.

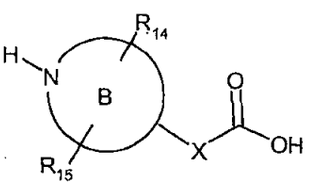
Los intermedios ya aludidos pueden prepararse, por ejemplo, mediante los métodos/procesos descritos a continuación.

b) Los compuestos de fórmula (II) en la cual R_1, R_2, R_3, R_4, B, Z, R_{14}, y R_{15} se definen como anteriormente, X es un enlace simple o un carbono, pueden prepararse haciendo reaccionar un compuesto de fórmula (IX)



(IX)

en la cual R_1, R_2, R_3, R_4 y Z se definen como para fórmula (I) de más arriba y L es un grupo saliente apropiado (tal como fluoro, cloro, bromo, yodo, triflato o tosilo), con un compuesto de la fórmula general (X),



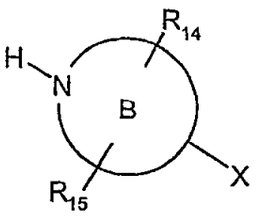
(X)

en la cual B, R_{14}, R_{15} se definen como anteriormente y X es un enlace simple o un carbono.

La reacción se lleva generalmente a cabo a temperaturas elevadas utilizando equipo estándar o un horno microondas de nodo simple. La

reacción puede llevarse a cabo en un disolvente inerte tal como etanol, DMA o una mezcla de disolventes tales como etanol-agua. Opcionalmente la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.

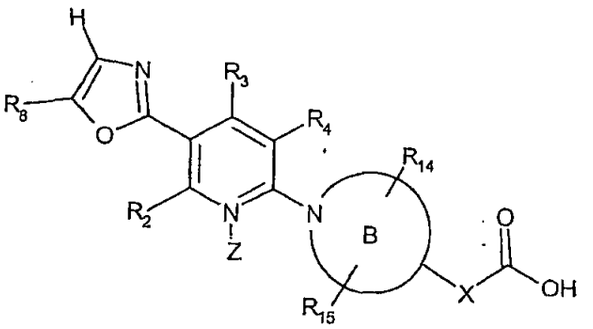
c) Compuestos de fórmula (IV) que se definen como anteriormente pueden prepararse haciendo reaccionar el compuesto correspondiente de fórmula (IX), que es como se define anteriormente, con un compuesto de fórmula (XI) en la cual B, R_{14}, R_{15} se definen como anteriormente, X es un nitrógeno o un enlace simple conectado a un nitrógeno que es un miembro del anillo B.



(XI)

La reacción se lleva generalmente a cabo a temperaturas elevadas utilizando equipo estándar o un horno microondas de nodo simple. La reacción puede llevarse a cabo en un disolvente inerte tal como etanol, DMA o una mezcla de disolventes tales como etanol-agua. Opcionalmente la reacción puede efectuarse en la presencia de una base orgánica tal como TEA o DIPEA.

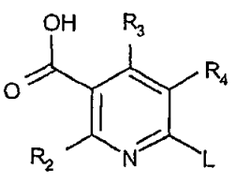
d) Síntesis de compuestos de la fórmula general (XXX),



(XXX)

en la cual R_2, R_3, R_4, B, R_8, R_{14} y R_{15} se definen como anteriormente y X es un carbono o un enlace simple comprende los siguientes pasos (d1-d5).

di) Hacer reaccionar los correspondientes compuestos de la fórmula general (X), la cual es como ya se definió, con un compuesto de la fórmula general (XXI)

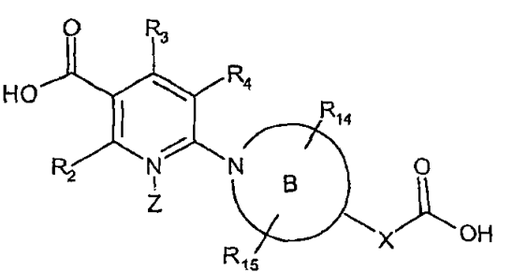


(XXI)

en la cual R_2, R_3 y R_4 se definen como para la fórmula I, y L es un grupo saliente apropiado, tal como cloro, bromo, yodo, triflato o tosilo, para producir un compuesto de fórmula (XXII).

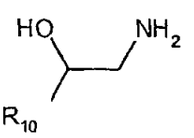
Las reacciones se llevan a cabo a temperaturas elevadas empleando equipo estándar o un horno microondas de nodo simple. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.

d2) Los compuestos de fórmula (XXII) pueden hacerse reaccionar



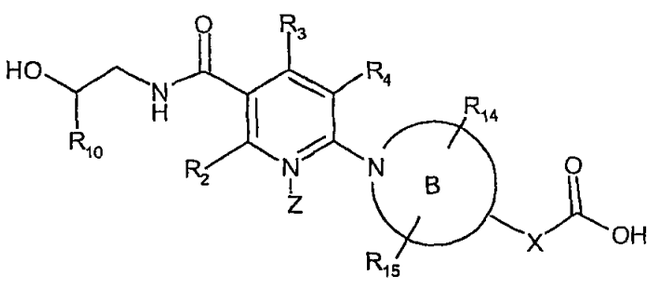
(XXII)

con un compuesto de la fórmula general (XXIII),



(XXIII)

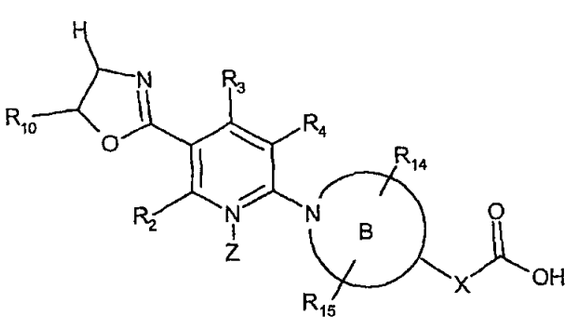
en la cual R_{10} es como ya se definió, para producir compuestos de la fórmula general (XXIV). Las reacciones se llevan a cabo usando condiciones estándar o en la presencia de EDCI o la combinación de EDCI y HOBT. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.



(XXIV)

d3) Este compuesto (XXIV) puede transformarse luego en un compuesto de la fórmula general (XX)

d4) La preparación de compuestos con la fórmula general (XX),



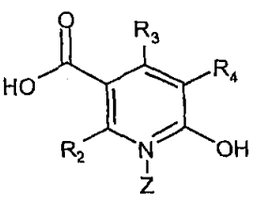
(XX)

en la cual R_2, R_3, R_4, B, R_{10}, R_{14} y R_{15} son como ya se definieron y X es un carbono o un enlace simple empleando métodos conocidos o un reactivo conocido tal como cloruro de metanosulfonilo. Opcionalmente la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA.

d5) Puede hacerse oxidando el correspondiente compuesto de la fórmula general (XX) en donde R_{10} es el mismo sustituyente que para R_8, empleando un reactivo de oxidación conocido tal como DDQ.

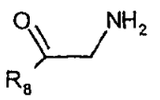
e) La preparación de compuestos de la fórmula general (XXX) comprende asimismo los siguientes pasos (*e1-e4*):

e1) Hacer reaccionar un compuesto de la fórmula general (XXXI),



(XXXI)

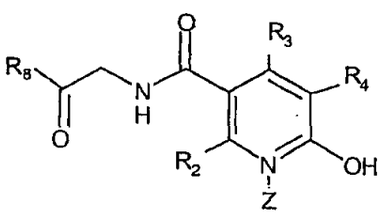
en la cual R_2, R_3 y R_4 se definen como para el compuesto (I) de más arriba, con un compuesto de la fórmula general (XXXII), en la cual R_8 es como ya se definió,



(XXXII)

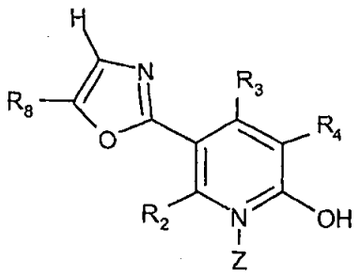
empleando condiciones estándar en la presencia de EDCI o la combinación de EDCI y HOBT. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA. Esta reacción produce un compuesto de la fórmula general (XXXIII).

e2) El compuesto de la fórmula general (XXXIII) obtenido



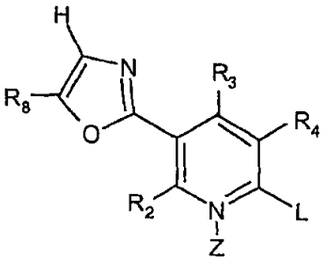
(XXXIII)

puede transformarse entonces en un compuesto de la fórmula general (XXXIV), en la cual R_2, R_3, R_4 y R_8 son como ya se definieron, empleando técnicas conocidas o utilizando un reactivo conocido tal como $POCl_3$.



(XXXIV)

e3) Un compuesto de la fórmula general (XXXIV) puede transformarse entonces en un compuesto de la fórmula general (XXXV),

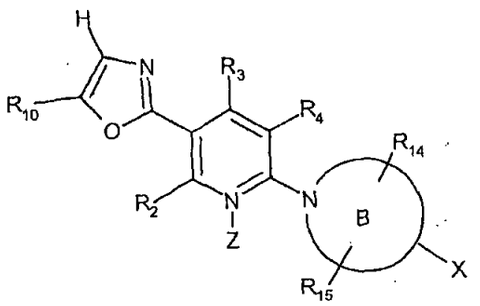


(XXXV)

en la cual R_2, R_3, R_4, R_8 son como ya se definieron y L es un grupo saliente adecuado, tal como cloro, bromo, yodo, triflato o tosilo, empleando técnicas conocidas o un reactivo tal como cloruro de oxalilo o cloruro de tionilo.

e4) El compuesto de fórmula (XXXV) puede hacerse reaccionar entonces con un compuesto de la fórmula general (X), el cual es como ya se definió, para producir un compuesto de la fórmula general (XXX), ya definido. Las reacciones se llevan a cabo a temperaturas elevadas empleando equipo estándar o un horno microondas de nodo simple. Opcionalmente, las reacciones pueden llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.

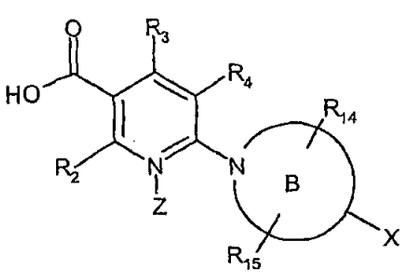
f) Preparación de compuestos de la fórmula general (XXXVI),



(XXXVI)

en la cual R_2, R_3, R_4, B, R_{10}, R_{14} y R_{15} son como ya se definieron, X es un nitrógeno o un enlace simple conectado a un nitrógeno que es un miembro del anillo B, comprende los siguientes pasos (*f1-f4*):

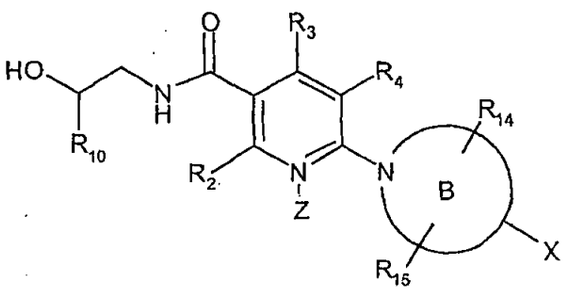
f1) Hacer reaccionar un compuesto de la fórmula general (XI), la cual es como ya se definió, con un compuesto de la fórmula general (XXI), la cual es como ya se definió, para producir un compuesto de la fórmula general (XXVIII).



(XXVIII)

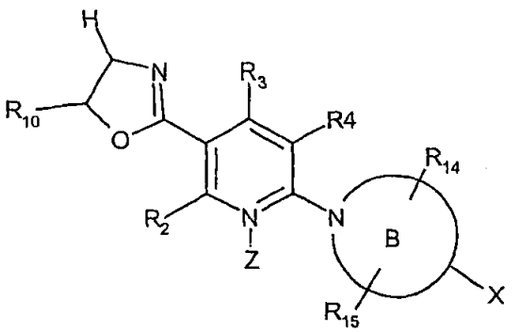
Las reacciones se llevan a cabo a temperaturas elevadas empleando equipo estándar o un horno microondas de nodo simple. Opcionalmente la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.

f2) El compuesto de fórmula (XXVIII) puede hacerse reaccionar con un compuesto de fórmula (XXIII), la cual es como ya se definió, para producir compuestos de la fórmula general (XXIX). Las reacciones se llevan a cabo usando condiciones estándar o en la presencia de EDCI, o la combinación de EDCI y HOBT. Opcionalmente las reacciones pueden llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.



(XXIX)

f3) Este compuesto puede transformarse entonces en un compuesto de la fórmula general (XXVI), en la cual R_2, R_3, R_4, B, R_{10}, R_{14} y R_{15}, son como ya se definieron,



(XXVI)

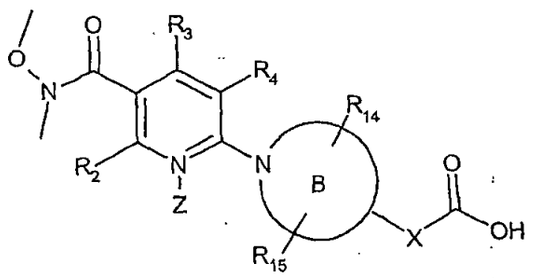
X es un nitrógeno o un hidrógeno conectado a un nitrógeno, el cual es un miembro del anillo B, empleando métodos conocidos o un reactivo adecuado tal como cloruro de metanosulfonilo. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA.

f4) (XXXVI) puede prepararse entonces oxidando un compuesto de la fórmula general (XXVI), el cual es como ya se definió. La reacción puede efectuarse empleando condiciones estándar o un reactivo como DDQ.

Compuestos de la fórmula general (II), en la cual R_1 es $R_7C(O)$, R_2, R_3, R_4, B, R_{14} y R_{15} son como ya se definieron, X es un enlace simple, comprenden los siguientes pasos (*g1-g2*):

g1) Hacer reaccionar un compuesto de la fórmula general (XXII), ya descrito, con N,O-dimetilhidroxilamina. La reacción puede llevarse a cabo

empleando reactivos conocidos como CDI para producir un compuesto de la fórmula general (XXXVIII).

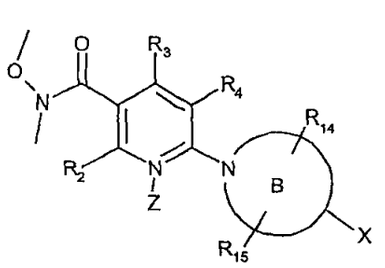


(XXXVIII)

g2) Hacer reaccionar compuestos de la fórmula general (XXXVIII), ya definidos, con un reactivo de la fórmula general R_7-MgX, en la cual R_7 es como ya se definió y X es un halógeno, o un reactivo de la fórmula R_7-M, en la cual M es un metal ejemplificado por Zn y Li.

Compuestos de la fórmula general (IV), en la cual R_1 es $R_7C(O)$, R_2, R_3, R_4, B, R_{14} y R_{15} son como ya se definieron, X es un nitrógeno o un enlace simple conectado a un nitrógeno, el cual es un miembro del anillo B, comprenden los siguientes pasos (*h1-h2*).

h1) Hacer reaccionar un compuesto de la fórmula general (XXVIII), ya definido, con N,O-dimetilhidroxilamina. La reacción puede llevarse a cabo empleando reactivos conocidos como CDI para producir un compuesto de la fórmula general (XLI).



(XLI)

h2) Un compuesto de la fórmula general (XLI), el cual es como ya se definió, puede hacerse reaccionar con un reactivo de la fórmula general R_7-MgX, en la cual E_7 es como ya se definió y X es un halógeno, o un reactivo de la fórmula R_7-M, en la cual M es un metal ejemplificado por Zn y Li.

Compuestos de la fórmula general (VIII) pueden formarse en uno de los procesos (*i1-i5*). Los compuestos de fórmula (VIII), en la cual R_5 es hidrógeno, se aislan ventajosamente como un ión híbrido. Un nitrógeno del anillo de compuestos de fórmula (X) y (XI), empleados en los siguientes pasos, pueden protegerse con un grupo protector tal como t-butiloxicarbonilo.

i1) Compuestos de la fórmula general (VIII), en la cual B, R_5, R_{14}, R_{15} R^c y R^d son como ya se definieron, X es un enlace simple o un carbono, pueden formarse haciendo reaccionar un compuesto de fórmula (X) con un compuesto de fórmula (III). La reacción se lleva generalmente a cabo en un disolvente orgánico inerte, tal como diclorometano a temperatura ambiente. La reacción puede llevarse a cabo empleando condiciones estándar o en la presencia de EDCI, o la combinación de EDCI y HOBT. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como trietilamina o DIPEA.

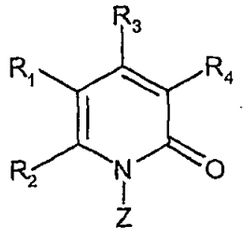
i2) Compuestos de la fórmula general (VIII), en la cual B, R_5, R_{14}, R_{15}, R^c y R^d son como ya se definieron, X es un enlace simple o un carbono, pueden formarse igualmente haciendo reaccionar un compuesto de fórmula (X) con un compuesto de fórmula (III), en la cual se protege el nitrógeno en el anillo B, por ejemplo, con t-butiloxicarbonilo. La reacción se lleva generalmente a cabo en un disolvente orgánico inerte tal como THF. La reacción puede llevarse a cabo empleando condiciones estándar o en la presencia de TBTU. Opcionalmente, la reacción puede llevarse a cabo en la presencia de una base orgánica tal como trietilamina o DIPEA. Ventajosamente, puede emplearse un reactivo tal como LiCl. Cuando el producto contiene un t-butiloxicarbonilo, éste puede retirarse empleando procedimientos estándar o en la presencia de ácido fórmico. Cuando R_5 es hidrógeno, el compuesto (VIII) puede aislarse como un ión híbrido.

i3) Compuestos de la fórmula general (VIII), en la cual R_5 es hidrógeno, B, R_{14}, R_{15}, R^c y R^d son como ya se definieron, X es un nitrógeno o un enlace simple conectado a un nitrógeno, el cual es un miembro del anillo B, pueden formarse haciendo reaccionar un compuesto de fórmula (XI), ya definido, con un compuesto de fórmula (V), ya definido. La reacción se lleva generalmente a cabo en un disolvente inerte tal como THF. La reacción puede efectuarse también en la presencia de una base orgánica tal como trietilamina o DIPEA.

i4) Compuestos de la fórmula general (VIII), en la cual B, R_5, R_{14}, R_{15}, R^c y R^d ya definidos, X es un nitrógeno o un enlace simple conectado a un nitrógeno, el cual es un miembro del anillo B, pueden formarse igualmente haciendo reaccionar un compuesto de fórmula (XI) con un compuesto de fórmula (VI), el cual es como ya se definió. La reacción se lleva generalmente a cabo en un disolvente tal como DMA. Esta reacción se efectúa también en la presencia de una base orgánica tal como trietilamina o DIPEA

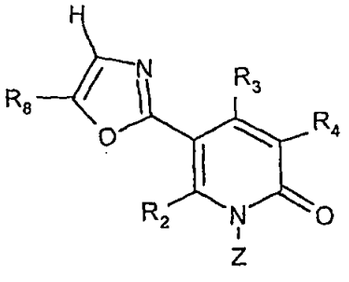
i5) Un compuesto de fórmula (VIII), que se protege con t-butoxicarbonilo puede transformarse en un compuesto sin el grupo protector empleando procedimientos estándar o un reactivo tal como ácido fórmico.

(j) Compuestos de la fórmula general (VII), los cuales son como ya se definieron, pueden formarse haciendo reaccionar un compuesto de fórmula (XLVI), empleando condiciones estándar o con un agente clorante tal como cloruro de tionilo o $POCl_3$. Ventajosamente, puede emplearse dimetilformamida. La reacción puede realizarse en un disolvente inerte. Ventajosamente, el disolvente inerte es tolueno.



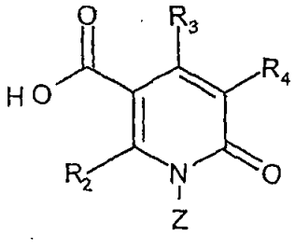
(XLVI)

La preparación de compuestos de la fórmula general (XLVII), la cual es como ya se definió, comprenden los siguientes pasos (*k1-k3*):



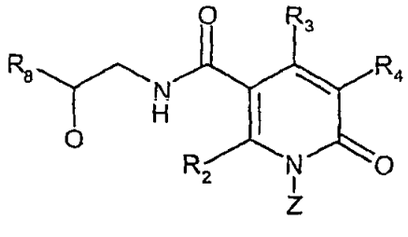
(XLVII)

k1) Hacer reaccionar un compuesto de la fórmula general (XLVIII)



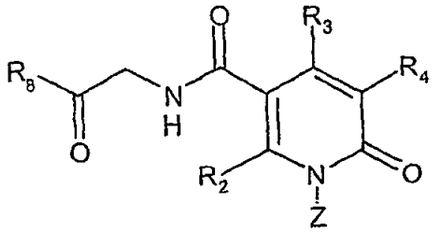
(XLVIII)

con un compuesto de la fórmula general (XXIII), el cual tiene R_8 en lugar de R_{10}, ya definido por lo demás, para producir un compuesto de la fórmula (IL). La reacción se lleva generalmente a cabo en DCM a temperatura ambiente. La reacción puede llevarse a cabo empleando condiciones estándar o en la presencia de EDCI, la combinación de EDCI y HOBT. Opcionalmente la reacción puede llevarse a cabo en la presencia de una base orgánica tal como TEA o DIPEA.



(IL)

k2) El compuesto de fórmula (IL) puede transformarse en un compuesto (L) empleando condiciones estándar o un agente oxidante tal como una mezcla de cloruro de oxalilo y DMSO.



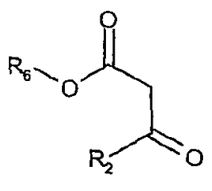
(L)

k3) El compuesto de fórmula (L) puede transformarse entonces en un compuesto de la fórmula general (XLVII), empleando condiciones estándar o en la presencia de hidróxido de (metoxicarbonilsulfamoil)trietilamonio (reactivo de Burgess). Generalmente la reacción se lleva a cabo en un disolvente inerte tal como THF. La reacción se efectúa a temperaturas elevadas, empleando equipo estándar o un horno microondas de nodo simple.

Compuestos de la fórmula general (III) pueden formarse haciendo reaccionar el correspondiente cloruro de sulfonilo, empleando métodos conocidos con amoníaco en un disolvente inerte tal como metanol.

1) Preparación de compuestos de la fórmula general (XLVIII), la cual es como ya se definió, excepto para R_3 que es hidrógeno, comprende los siguientes pasos (l_1 –l_3);

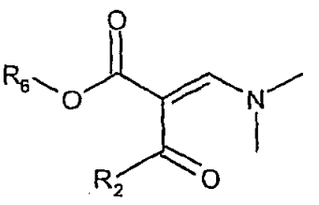
l1) Hacer reaccionar un compuesto de la fórmula (LI), en la cual R_2 y R_5 se definen como para la fórmula (I), con dimetoxi-N,N-dimetilmetanoamina para formar un



(LI)

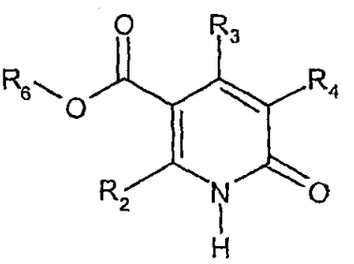
compuesto de fórmula (LII).

l2) Este compuesto (LII) puede hacerse reaccionar posteriormente con un compuesto de la



(LII)

fórmula general $R_4CH_2C(O)NH_2$, en la cual R_4 se define como para fórmula (I) para producir un compuesto de la fórmula general (LIII). Generalmente la reacción se efectúa en un disolvente inerte tal como etanol, opcionalmente en la presencia de una base fuerte tal como etóxido de sodio.

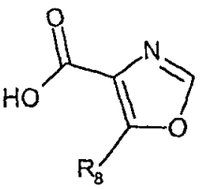


(LIII)

(l3) Un compuesto de la fórmula general (LIII) puede transformarse entonces en un compuesto de la fórmula general (XLVHI). La reacción se realiza generalmente en un disolvente prótico tal como agua, junto con un co-disolvente tal como THF o metanol. La reacción puede llevarse a cabo empleando reactivos estándar o en la presencia de LiOH, NaOH o KOH.

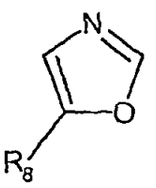
(m) La formación de un compuesto de la fórmula general (XXX), la cual es como ya se definió, puede hacerse por la siguiente síntesis:

m1) Un compuesto de la fórmula general (LIV), donde R_8 se define como para fórmula (I) de más arriba, puede



(LIV)

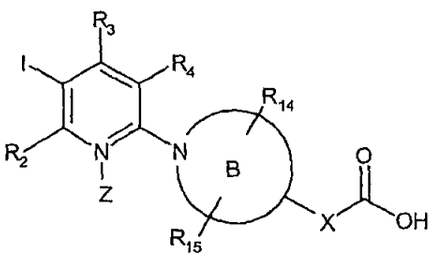
transformarse en un compuesto de la fórmula (LV)



(LV)

empleando condiciones estándar o usando Cu(II)O y quinolina.

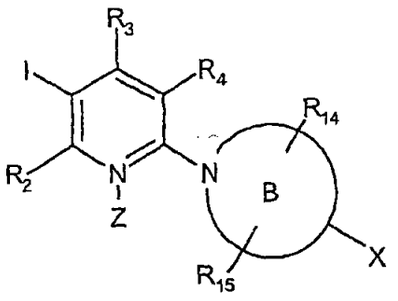
m2) El compuesto de la fórmula general (LV) puede hacerse reaccionar con un compuesto de la fórmula general (LVI) en



(LVI)

la cual R_2, R_3, R_4, B, R_{14} y R_{15} se definen como para la fórmula (I) y X es un carbono o un enlace simple, para producir compuestos de la fórmula general (XXX). La reacción se realiza generalmente en un disolvente inerte tal como THF, bajo una atmósfera inerte. La reacción puede llevarse a cabo empleando condiciones estándar o en la presencia de alquilLi tal como BuLi, $ZnCl_2$, $Pd(Ph_3)_4$.

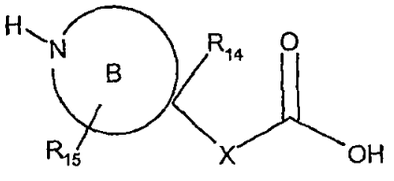
(*n*) Compuestos de la fórmula general (XXXVI) pueden prepararse igualmente por el siguiente paso:



(LVII)

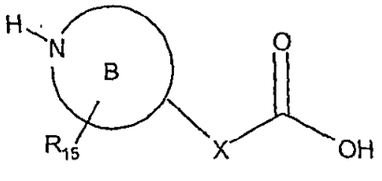
n1) Hacer reaccionar un compuesto de la fórmula general (LV), la cual es como ya se definió, con un compuesto de la fórmula general (LVII), en la cual R_2, R_3, R_4, B, R_{14} y R_{15} se definen como en la anterior fórmula (I), X es un nitrógeno o un enlace simple conectado a un nitrógeno, que es un miembro del anillo B.

o) La preparación de compuestos de la fórmula general (LVIII), en la cual R_{14} y R_{15} se definen como para la fórmula (I), con la excepción que R_{14} se conecta al mismo átomo que X, y X se define como un enlace simple, comprende el siguiente paso:



(LVIII)

o1) Hacer reaccionar el correspondiente (LIX) con R_{14}-L, en donde L es un grupo saliente apropiado, tal como cloro, bromo, yodo,



(LIX)

triflato o tosilo para formar compuestos de la fórmula general (LVIII), empleando condiciones estándar o en la presencia de una mezcla de BuLi y diisopropilamina.

La preparación de compuestos de la fórmula (III) comprende los siguientes procesos (*p1-p3*):

p1) Un compuesto de la fórmula LR^cR^d en donde L es un grupo saliente apropiado, tal como cloro, bromo, yodo podría transformarse en el correspondiente compuesto (III) empleando una secuencia de reacciones utilizando primero SMOPS* (*Baskin and Wang. Tetrahedron Letters, 2002, 43, 8479-83. Véase especialmente la página 8480, columna de la izquierda.), seguido por hidrólisis empleando una base como NaOMe en un disolvente inerte como DMSO a temperatura ambiente, seguido por el tratamiento con NH_2OSO_3H y NaOAc para producir un compuesto de fórmula (III).

p2) Un compuesto de la fórmula $LSO_2R^cR^d$, en donde L es un grupo saliente apropiado, tal como cloro, bromo, yodo podría hacerse reaccionar con hidróxido de amonio o H_2NR_5 en un disolvente inerte tal como DCM para producir un compuesto de fórmula (III).

p3) Un compuesto de la fórmula LR^cR^d, en donde L es un grupo saliente apropiado, tal como cloro, bromo, yodo podría transformarse en el correspondiente compuesto (III), empleando una secuencia de reacciones, primeramente $NaSO_3$, seguido por el uso de un reactivo tal como PCl_5, $POCl_3$ o $SOCl_2$, seguido por hidróxido de amonio o H_2NR_5 para producir un compuesto de fórmula (III).

En cualquier etapa de la síntesis de piridinas amina sustituidas, un sustituyente cloro en la posición 2, 4 ó 6 de la piridina puede reemplazarse con azida usando técnicas conocidas. La azida puede reducirse a la amina correspondiente. Estas aminas pueden alquilarse o acilarse posteriormente usando métodos conocidos o con un alquilhaluro o acilhaluro, respectivamente.

Las personas expertas en el arte advertirán que un ácido puede transformarse en el éster activado correspondiente tal como un cloruro ácido, seguido por reacción con un tiol, $R_{16}SH$ para producir tioésteres, $R_{16}SC(O)$.

Las personas expertas en el arte observarán que un ácido puede transformarse en el correspondiente éster activado tal como un cloruro ácido, seguido por la reacción con un alcohol, R_6OH para producir ésteres, $R_6OC(O)$.

Las personas expertas en el arte notarán que un compuesto de fórmula (III) podría alquilarse en el átomo de carbono en la posición α en la sulfonamida empleando un haluro alquílico, preferiblemente bajo condiciones básicas empleando una base fuerte tal como hidruro de sodio.

Las personas expertas en el arte se darán cuenta que un sustituyente nitrógeno en la posición 3 de una piridina podría reemplazarse por una cadena tioéter, $R_{17}S$-, usando técnicas conocidas o $R_{17}SSR_{17}$ y nitrito de *terc*-butilo.

Las personas expertas en el arte advertirán que una tiocetona podría elaborarse de la cetona correspondiente usando técnicas conocidas o utilizando un reactivo de Lawesson.

Las personas expertas en el arte observarán que un N-óxido de piridina podría formarse de una piridina empleando un agente oxidante tal como peróxido de hidrógeno de urea o peróxido de hidrógeno, con o sin la presencia de anhídrido trifluoroacético.

Los compuestos de la invención pueden aislarse de sus mezclas de reacción usando técnicas convencionales.

Las personas expertas en el arte advertirán que, con el fin de obtener compuestos de la invención en una manera alternativa y, en algunas ocasiones, más conveniente, los pasos individuales del proceso antes mencionados pueden realizarse en un orden diferente, y/o las reacciones individuales puede efectuarse en una etapa diferente de la ruta general (es decir, pueden llevarse a cabo transformaciones químicas en intermedios diferentes a los asociados antes con una reacción particular).

Se advertirá por las personas expertas en el arte que los procesos descritos anteriormente y a partir de ahora para grupos funcionales de compuestos intermedios pueden necesitar protegerse por grupos protectores.

Grupos funcionales que es deseable proteger incluyen hidroxi, amino y ácido carboxílico. Grupos protectores adecuados para hidroxi incluyen grupos alquilo opcionalmente substituido y/o insaturado (por ejemplo, metilo, alilo, bencilo o *terc*-butilo), grupos trialquilsililo o diarilalquilsililo (por ejemplo, *t*-butildimetilsililo, *t*-butildifenilsililo o trimetilsililo) y tetrahidropiranilo. Grupos protectores apropiados para ácidos carboxílicos incluyen ésteres (C_1-C_6)alquílicos o bencílicos. Grupos protectores adecuados para amino incluyen *t*-butiloxicarbonilo, benciloxicarbonilo, 2-(trimetilsilil)etoximetilo o 2-trimetilsililetoxicarbonilo (Teoc).

La protección y desprotección de grupos funcionales puede tener lugar antes o después de cualquier reacción en los procesos ya mencionados.

Las personas expertas en el arte advertirán que, con el fin de obtener compuestos de la invención en una manera alternativa y, en algunas ocasiones, más conveniente, los pasos individuales del proceso antes mencionados pueden realizarse en un orden diferente, y/o las reacciones individuales puede efectuarse en una etapa diferente de la ruta general (es decir, pueden agregarse sustituyentes a y/o realizarse transformaciones

químicas en, intermedios diferentes a los antes mencionados en conjunción con una reacción particular). Esto puede invalidar, o hacer imprescindible, la necesidad de grupos protectores.

Las personas expertas en el arte advertirán que materiales de partida para cualquiera de los anteriores procesos pueden hallarse disponibles en el comercio en algunos casos.

Las personas expertas en el arte se darán cuenta que los procesos anteriores para algunos materiales de partida ya indicados podrían hallarse en el conocimiento común general.

El tipo de química implicado dictará la necesidad de grupos protectores, así como la secuencia para realizar la síntesis.

El uso de grupos protectores se describe completamente en "Protective groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), y "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M Wutz, Wiley-Interscience (1999).

Derivados protegidos de la invención pueden convertirse químicamente en compuestos de la invención usando técnicas estándar de desprotección (por ejemplo, bajo condiciones alcalinas o ácidas).

La persona experta en el arte advertirá igualmente que ciertos compuestos de fórmula (II)-(LIX) pueden denominarse también como "derivados protegidos".

Compuestos de la invención pueden contener asimismo uno o más átomos de carbono asimétricos y, en consecuencia, pueden exhibir isomerismo óptico y/o diastereoisomerismo. Los diastereoisómeros pueden separarse usando técnicas convencionales, por ejemplo, cromatografía. Los diferentes estereisómeros pueden aislarse mediante separación de una mezcla racémica, u otra, de los compuestos empleando técnicas convencionales, por ejemplo HPLC. Alternativamente, los isómeros ópticos deseados pueden elaborarse mediante reacción de los materiales de

partida apropiados, ópticamente activos, bajo condiciones que no causen racemización o epimerización, o mediante derivación, por ejemplo con un ácido homoquiral, seguido por separación de los derivados diastereoméricos por medios convencionales (por ejemplo, HPLC, cromatografía sobre gel o cristalización). Pueden introducirse también estereocentros por síntesis asimétrica, (por ejemplo, reacciones metaloorgánicas usando ligandos quirales). Todos los estereoisómeros se encuentran incluidos en el ámbito de la invención.

Todos los intermedios novedosos constituyen un aspecto adicional de la invención.

Sales de los compuestos de fórmula (I) pueden formarse haciendo reaccionar el ácido libre, o su sal, o la base libre, o su sal o derivado, con uno o más equivalentes de la base apropiada (por ejemplo hidróxido de amonio sustituido opcionalmente por C_1-C_6-alquilo, o un hidróxido de metal alcalino o alcalinotérreo) o ácido (por ejemplo un hidrohaluro (especialmente HCl), ácido sulfúrico, oxálico o fosfórico). La reacción puede llevarse a cabo en un disolvente o medio en el cual la sal es insoluble, o en un disolvente en el cual la sal es soluble, por ejemplo agua, etanol, tetrahidrofurano o éter dietílico, que puede retirarse *in vacuo*, o mediante secamiento por congelamiento. La reacción puede efectuarse asimismo en una resina de intercambio iónico. Se prefieren las sales no tóxicas fisiológicamente aceptables, aunque pueden ser útiles otras sales, por ejemplo en aislar o purificar el producto.

Datos Farmacológicos

La inhibición funcional del receptor $P2Y_{12}$ puede medirse mediante análisis *in vitro* usando membranas de células CHO transfectadas con $P2Y_{12}$, la metodología se detalla a continuación.

Inhibición funcional de señalización de $P2Y_{12}$ inducida por 2-Me-S-ADP: 5µg de membranas se diluyeron en 200 µl de 200mM NaCl, 1mM $MgCl_2$, 50mM HEPES (pH 7.4), 0.01% BSA, 30µg/ml saponina y 10µM GDP. A esto se añadió una concentración EC_{80} de agonista (2-metil-tio-

adenosina difosfato), la concentración requerida del compuesto de prueba y 0.1 μCi ^{35}S-GTPγS. Se dejó avanzar la reacción a 30°C durante 45 minutos. Seguidamente las muestras se transfirieron a filtros GF/B usando un cosechador de células y se lavaron con amortiguador de lavado (50mM Tris (pH 7.4), 5mM $MgCl_2$, 50mM NaCl). En seguida los filtros se cubrieron con agente de centelleo (***"scintilant"***) y se contaron con respecto a la cantidad de ^{35}S-GTPγS retenido por el filtro. La actividad máxima fue la determinada en la presencia del agonista, y la actividad mínima en la ausencia del agonista, luego de restar el valor determinado para actividad no específica. El efecto de compuestos en varias concentraciones se graficó de acuerdo con la ecuación

$y = A+((B-A)/(1+((C/x)^{\wedge}D)))$

e IC_{50} calculado donde

A es el límite inferior de la curva, es decir, el valor **y** mínimo final

B es el límite superior de la curva, es decir el valor **y** máximo final

C es el valor **x** en el centro de la curva. Esto representa el valor **log EC_{50}** cuando A + B = 100

D es el factor de la pendiente.

X representa los valores **X** conocidos originales.

Y representa los valores **Y** conocidos originales.

La mayoría de los compuestos de la invención tienen una actividad, cuando se prueban en el análisis descrito de inhibición funcional de la señalización P_2Y_{12} inducida por 2-Me-S-ADP, con una concentración de alrededor de 4 μM o menor.

Por ejemplo, los compuestos descritos en los Ejemplos 91 y 119 arrojaron el siguiente resultado de prueba en la inhibición funcional del análisis descrito de señalización de P_2Y_{12} inducida por 2-Me-S-ADP.

$IC_{50}(\mu M)^{a)}$

Ejemplo 91	0.46
Ejemplo 119	0.25

Los compuestos de la invención actúan como antagonistas de receptor $P2Y_{12}$ y, en consecuencia, son útiles en terapia. Por lo tanto, de acuerdo con un aspecto adicional de la invención se provee un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, para uso en terapia.

En un aspecto adicional se provee el uso de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, para la fabricación de un medicamento para tratamiento de un trastorno de agregación plaquetaria. En otro aspecto de la invención se provee el uso de un compuesto de fórmula (I), o su sal farmacéuticamente aceptable, para la fabricación de un medicamento para la inhibición del receptor $P2Y_{12}$.

Los compuestos son útiles en terapia, especialmente terapia complementaria; particularmente, son indicados para uso como: inhibidores de activación plaquetaria, agregación y desgranulación, promotores de desagregación plaquetaria, agentes anti-trombóticos o en el tratamiento de profilaxis de angina inestable, angioplastia coronaria (PTCA, angioplastia coronaria percutánea transluminal), infarto del miocardio, peritrombólisis, complicaciones trombóticas arteriales primarias de aterosclerosis tal como apoplejía trombótica o embólica, ataques isquémicos transitorios, enfermedad vascular periférica, infarto del miocardio con o sin trombólisis, complicaciones arteriales debidas a intervenciones en enfermedad aterosclerótica tal como angioplastia, endoarteriectomía, colocación de endoprótesis vascular (***"stent placement"***), cirugía de injerto coronario y vascular, complicaciones trombóticas de lesión quirúrgica o mecánica tal como recuperación de tejido a raíz de trauma accidental o quirúrgico, cirugía reconstructiva incluidos colgajos de piel y músculo, afecciones con un componente de consumo trombótico/plaquetario difuso tales como coagulación intravascular diseminada, púrpura trombocitopénica trombótica, síndrome urémico hemolítico, complicaciones trombóticas de septicemia, síndrome dineico agudo del adulto, síndrome anti-fosfolípido,

trombocitopenia inducida por heparina y pre-eclampsia/eclampsia, o trombosis venosa tal como trombosis de vena profunda, enfermedad veno-oclusiva, enfermedades hematológicas tales como enfermedad mieloproliferativa, incluida trombocitemia, enfermedad drepanocítica; o en la prevención de activación plaquetaria inducida mecánicamente *in vivo*, tal como derivación cardio-pulmonar y oxigenación de membrana extracorporal (prevención de microtromboembolismo), activación plaquetaria inducida mecánicamente *in vitro*, tal como el empleo en la preservación de productos sanguíneos, por ejemplo concentrados plaquetarios, u oclusión de anastomosis tal como en diálisis renal y plasmaféresis, trombosis secundaria a lesión/inflamación vascular tal como vasculitis, arteritis, glomerulonefritis, síndrome del colon irritable y rechazo de injerto de órganos, afecciones tales como migraña, fenómeno de Raynaud, trastornos en los cuales las plaquetas pueden contribuir al proceso de enfermedad inflamatoria fundamental en la pared vascular, tal como formación/progresión de placa ateromatosa, stenosis/restenosis y en otras afecciones inflamatorias tales como asma, en las cuales se encuentran implicados plaquetas y factores derivados de plaquetas en el proceso de enfermedad inmunológica.

De acuerdo con la invención se provee asimismo el uso de un compuesto de acuerdo con la invención en la fabricación de un medicamento para el tratamiento de los trastornos anteriores. En particular, los compuestos de la invención son útiles para tratar infarto del miocardio, apoplejía trombótica, ataques isquémicos transitorios, vasculopatía periférica y angina, especialmente angina inestable. La invención contempla asimismo un método de tratamiento de los trastornos anteriores, que comprende administrar a un paciente que padece de tal trastorno, una cantidad terapéuticamente efectiva de un compuesto de acuerdo con la invención.

En un aspecto adicional la invención provee una composición farmacéutica que comprende un compuesto de fórmula (I), o su sal

farmacéuticamente aceptable, junto con un diluyente, coadyuvante y/o excipiente farmacéuticamente aceptables.

Los compuestos pueden administrarse tópicamente, por ejemplo al pulmón y/o las vías respiratorias, en la forma de soluciones, suspensiones, aerosoles HFA y formulaciones en polvo seco; o sistémicamente, por ejemplo, mediante administración oral en la forma de tabletas, píldoras, cápsulas, jarabes, polvos o gránulos, o mediante administración parenteral en la forma de soluciones o suspensiones parenterales estériles, mediante administración subcutánea, o mediante administración rectal en la forma de supositorios o por vía transdérmica.

Los compuestos de la invención pueden administrarse en sí mismos o como una composición farmacéutica que comprende el compuesto de la invención en combinación con un diluyente, coadyuvante o excipiente farmacéuticamente aceptables. Las composiciones particularmente preferidas son aquellas que no contienen material capaz de causar una reacción adversa, por ejemplo, alérgica.

Formulaciones en polvo seco y aerosoles HFA presurizados de los compuestos de la invención pueden administrarse mediante inhalación oral o nasal. Para la inhalación, el compuesto se encuentra preferiblemente en forma finamente dividida. Los compuestos de la invención pueden administrarse asimismo mediante un inhalador de polvo seco. El inhalador puede ser un inhalador de dosis unitaria o dosis múltiples, y puede ser un inhalador de polvo seco accionado por la respiración.

Una posibilidad es mezclar un compuesto finamente dividido con una sustancia excipiente, por ejemplo un mono-, di- o polisacárido, un alcohol de azúcar u otro poliol. Los excipientes apropiados incluyen azúcares y almidón. Alternativamente, el compuesto finamente dividido puede recubrirse con otra sustancia. La mezcla de polvo puede dispensarse también en cápsulas de gelatina duras, conteniendo cada una la dosis deseada del compuesto activo.

Otra posibilidad es procesar el polvo finamente dividido en esferas, que se rompen durante el procedimiento de inhalación. Este polvo

esferoide puede envasarse en el depósito del medicamento de un inhalador multidosis, por ejemplo el conocido como el Turbuhaler®, en el cual una unidad dosificadora cuantifica la dosis deseada, que se inhala luego por el paciente. Con este sistema, el compuesto activo, con o sin una sustancia excipiente, se administra al paciente.

La composición farmacéutica, que comprende el compuesto de la invención, puede estar convenientemente en la forma de tabletas, píldoras, cápsulas, jarabes, polvos o gránulos para administración oral; soluciones parenterales o subcutáneas estériles, suspensiones para administración parenteral o supositorios para administración rectal.

Para administración oral el compuesto activo puede mezclarse con un coadyuvante o excipiente, por ejemplo lactosa, sacarosa, sorbitol, mannitol, almidones tales como almidón de papa, almidón de maíz o amilopectina, derivados de celulosa, un aglutinante tal como gelatina o polivinilpirrolidona, y un lubricante tal como estearato de magnesio, estearato de calcio, polietilén glicoles, ceras, parafina, y similares, y luego comprimirse en tabletas. Si se requieren tabletas recubiertas, los núcleos, preparados como ya se describió, pueden recubrirse con una solución de azúcar concentrado, que puede contener por ejemplo goma arábiga, gelatina, talco, dióxido de titanio, y similares. Alternativamente, la tableta puede recubrirse con un polímero apropiado disuelto en un disolvente fácilmente volátil o en un disolvente acuoso.

Para la preparación de cápsulas de gelatina blandas, el compuesto pude mezclarse con, por ejemplo, un aceite vegetal o polietilén glicol. Las cápsulas de gelatina duras pueden contener gránulos del compuesto usando los excipientes ya mencionados para tabletas, por ejemplo lactosa, sacarosa, sorbitol, mannitol, almidón, derivados de celulosa o gelatina. Asimismo formulaciones líquidas o semisólidas del medicamento pueden envasarse en cápsulas de gelatina duras.

Preparaciones líquidas para aplicación oral pueden estar en la forma de jarabes o suspensiones, por ejemplo soluciones que contienen el compuesto, siendo el balance azúcar y una mezcla de etanol, agua, glicerol

y propilén glicol. Opcionalmente, tales preparaciones líquidas pueden contener agentes colorantes, agentes saborizantes, sacarina y carboximetilcelulosa como agente espesante u otros excipientes conocidos por los expertos en el arte.

La invención se ilustrará con más detalle en los siguientes ejemplos no limitantes:

Ejemplos

Procedimiento Experimental General

Los espectros de masa se registraron en un espectrómetro de masa con trampa de iones Finnigan LCQ Duo equipado con una interfase de electroaspersión (LC-MS) o sistema LC-MS conformado por un Waters ZQ usando un sistema LC-Agilent 1100 LC.

Las mediciones ^{1}HNMR se llevaron a cabo en un espectrómetro Varian Mercury VX 400, que operaba con una frecuencia ^{1}H de 400 y espectrómetros Varian UNITY plus 400, 500 y 600, que operaban a frecuencias ^{1}H de 400, 500 y 600 respectivamente. Los desplazamientos químicos se dan en ppm con el disolvente como estándar interno. Se realizó cromatografía usando gel de sílice Biotage 405, 40M, 12i ó gel de sílice Merck 60 (0.063-0.200mm). La cromatografía rápida se efectuó usando columnas de plástico o vidrio estándar o un sistema Biotage Horizon. Las separaciones por HPLC se llevaron a cabo en sistemas Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm o Waters Delta Prep, usando columnas Kromasil C8, 10 μm. Las reacciones se efectuaron en un reactor de microondas Personal Chemistry Smith Creator, Smith synthesizer o un Emrys Optimizer.

Listado de las abreviaturas usadas:

Abreviatura	Explicación
AcOH	Ácido acético
Aq	Acuoso
Br	Amplio
Salmuera	Una solución saturada de cloruro de sodio en agua
BSA	Albúmina sérica bovina
CDI	Carbonildiimidazol
d	Doblete
DCE	1,2-Dicloroetano
DCM	Diclorometano
DDQ	2,3-Dicloro-5,6-diciano-1,4-benzoquinona
DIEA	N,N-Diisopropiletilamina
DIPEA	N,N-Diisopropiletilamina
DMA	N,N-Dimetilacetamida
DMAP	N,N-dimetilpiridin-4-amina
DMF	N,N-dimetilformamida
DMSO	Sulfóxido de dimetilo
EDCI	Clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcaxbodiimida
EtOAc	Acetato de etilo
EtOH	Etanol
HATU	Hexafluorofosfato de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio
HEPES	Ácido [4-(2-hidroxietil)-1-piperazinetanosulfónico
HFA	Hidrofluoroalcanos
HOAc	Ácido acético
HOBT	1-Hidroxibenzotriazol
HPLC	Cromatografía líquida de alta resolución
Hz	Hertz

J	Constante de acoplamiento
LDA	Diisopropilamida de litio
M	Multiplete
m-CPBA	Ácido *meta*-chloroperoxibenzoico
MeOH	Metanol
MHz	Megahertz
mL	Mililitro
MS	Espectros de masa
NBS	1-Bromopirrolidin-2,5-dion-(N-bromo succinimida)
NCS	1-cloropirrolidin-2,5-diona
q	Cuartete
r.t	Temperatura ambiente/de la sala
s	Singlete
SMOPS	3-metoxi-3-oxopropano-1-sulfonato de sodio
t	triplete
TB	Amortiguador Tyrodes
TBTU	Tetrafluoroborato de N-[(1H-1,2,3-benzotriazol-1-iloxi)(dimetilamino)metilen]-N-metilmetanaminio
TEA	Trietilamina
TFA	Ácido trifluoroacético
THF	Tetrahidrofurano

Sulfonamidas

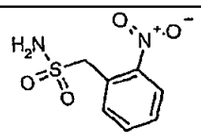
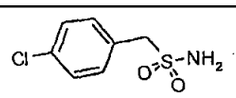
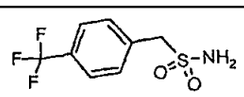
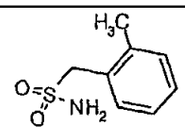
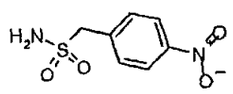
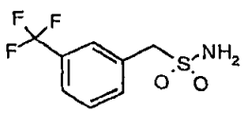
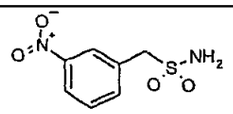
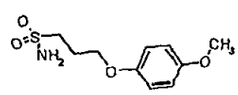
Síntesis de sulfonamidas

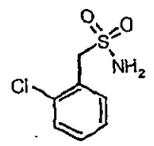
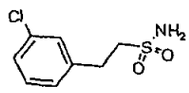
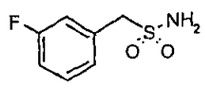
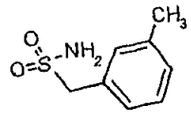
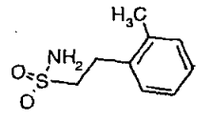
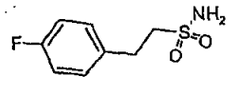
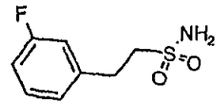
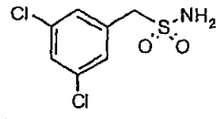
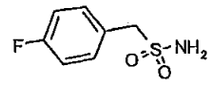
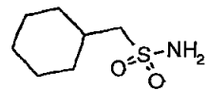
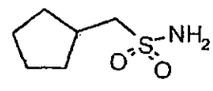
Cada una de las siguientes sustancias se elaboraron haciendo reaccionar el cloruro de sulfonilo correspondiente (0.75 mmol) con una solución saturada de amoníaco en MeOH (5 mL). Luego de la evaporación del amoníaco y MeOH, los residuos se disolvieron en MeOH (5 mL) y se agregaron unas cuantas gotas de DMF (2 mL) para disolver las mezclas de reacción. Las soluciones se filtraron luego separadamente a través de ISOLUTE SCX-2,

(cartucho 25 mL), que contenía resina ácida de intercambio iónico (ácido propilsulfónico tipo, 5 g). Se utilizó MeOH (16 mL) para enjuagar el producto de la resina. Luego del retiro del disolvente cada uno de los productos se utilizó sin purificación posterior, como se describe en el siguiente Método A.

Las sulfonamidas hechas mediante este procedimiento se enumeran en la Tabla 1. Otras sulfonamidas se elaboraron *mediante* métodos descritos en los Ejemplos o métodos similares a los descritos.

Tabla 1

Productos	**Nombre del compuesto**	**MW**	**Rendimiento: crudo**	
			mg	**%**
	1-(2-nitrofenil)metanosulfonamida	216.22	222	134%
	1-(4-clorofenil)metanosulfonamida	205.66	212	129%
	1-[4-(trifluorometil)fenil]metanosulfonamida	239.22	114	123%
	1-(2-metilfenil)metanosulfonamida	185.25	10	7%
	1-(4-nitrofenil)metanosulfonamida	216.22	198	119%
	1-[3-(trifluorometil)fenil]metanosulfonamida	239.22	210	114%
	1-(3-nitrofenil)metanosulfonamida	216.22	194	118%
	3-(4-metoxifenoxi)propano-sulfonamida	245.30	210	113%

	1-(2-clorofenil)metanosulfonamida	205.66	200	122%
	2-(3-clorofenil)etanosulfonamida	219.69	204	119%
	1-(3-fluorofenil)metanosulfonamida	189.21	192	130%
	1-(3-metilfenil)metanosulfonamida	185.25	284	196%
	2- (2-metilfenil)etanosulfonamida	199.27	324	185%
	2-(4-fluorofenil)etanosulfonamida	203.24	164	106%
	2-(3-fluorofenil)etanosulfonamida	203.24	176	111%
	1-(3,5-diclorofenil)metanosulfonamida	240.11	192	109%
	1-(4-fluorofenil)metanosulfonamida	189.21	156	108%
	1–ciclohexilmetanosulfonamida	177.27	134	95%
	1– ciclopentilmetanosulfonamida	163.24	148	108%

Síntesis de los Ejemplos

Método A:

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (Véase Ejemplo l(d)) (1 Eq), sulfonamida (1.48 Eq, la cantidad

y la estructura de la sulfonamida utilizada se especifica en cada uno de los siguientes Ejemplos) y DIPEA (5 Eq) se agitó en DMF (8 mL/mmol del ácido utilizado). HATU (1.05 Eq) se disolvió en DMF (4 mL/mmol del ácido utilizado), se agregó y la reacción se agitó a temperatura de la sala de un día para otro. El disolvente se retiró *in vacuo* y la mezcla cruda de reacción se disolvió en DMSO (1 mL) y se purificó mediante HPLC preparativa (Kromasil C8, partículas de 5µm, columna 100x21.2mm, Eluyente A: 100% acetonitrilo, Eluyente B: 0,1M acetato de amonio en agua que contenía 5% acetonitrilo, caudal 30 mL / min, empleando una gradiente cada vez mayor de acetonitrilo durante 8 minutos para proporcionar los productos luego de la evaporación de los disolventes).

Método B

A una solución de 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.21mmol) o ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.21 mmol) DCM (2mL) se agregaron TBTU 0.25 mmol) y DIPEA (1.05) mmol. La mezcla de reacción se agitó durante 10 minutos, seguida por la adición sulfonamida (0.25 mmol), por ejemplo de 5-clorotiofen-3-sulfonamida. La mezcla de reacción se agitó de un día para otro, seguida por la adición 0.1 M $KHSO_4$ (2mL), la fase orgánica se aisló y la mezcla cruda de reacción se sometió a HPLC preparativa (véase más adelante en cuanto a los detalles) con el fin de aislar el producto deseado, por ejemplo etil 6-[4-({[(5-cloro-3-tienil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato.

El sistema de HPLC preparativa utilizado fue un sistema de purificación Waters Fraction Lynx con columnas 5mm 20x100 mm Kromasil C8. La fase móvil empleada fueron gradientes variables de CH_3CN y 0.1 M de amortiguador NH_4OAc(aq). El caudal fue de 30 mL/minuto. Se usó recolección de fracciones desencadenada por MS. Los espectros de masa se registraron en un Micromass ZQ single quadrupole o un Micromass Quattro micro, los dos equipados con una interfaz de electroaspersión neumáticamente asistida.

Método C

Una solución de ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.091 g, 0.3 mmol), DIPEA 0.074 g, 0.6 mmol) y TBTU (0.039 g, 0.3 mmol) en 1 eq. DCM/ 1 eq .DMF (2 mL) se agregó a sulfonamida (0.4 mmol), por ejemplo 4-(trifluorometil) bencenosulfonamida. La mezcla de reacción se agitó durante 48 horas, seguida por la adición de TBTU (0.013 g, 0.1 mmol). Después de 20 horas, los disolventes se retiraron *in vacuo*. La mezcla cruda de reacción se agregó a $NaHSO_4$ (2 mL, 1M) y debido a diferencias en solubilidad entre los productos, se utilizaron DCM y DCM/acetato de etilo para extracción. La fase orgánica se aisló y los disolventes se retiraron *in vacuo*. El material crudo se purificó usando HPLC preparativa (véase más adelante en cuanto a los detalles) con el fin de aislar el producto deseado, por ejemplo isopropil 5-ciano-2-metil-6-{3-[({[4-(trifluorometil) fenil]sulfonil}amino)carbonil] azetidin-1-il}nicotinato.

Ejemplo 1

Etil éster de ácido 5-ciano-6-[3-(2-metoxicarbonil-fenilmetanosulfonil aminocarbonil)-azetidin-1-il]-2-metil-nicotínico

(a) Etil 2-((dimetilamino)metilen)-3-oxobutanoato

1,1-Dimetoxi-N,N-dimetilmetanamina (500 g, 4195 mmol) se agregó a etil 3-oxobutanoato (461.6 g, 3547 mmol) bajo una atmósfera de nitrógeno a temperatura de la sala durante 13 minutos (exoterma débil). La solución roja anaranjada se agitó durante 22 horas y se concentró *in vacuo*. El residuo se co-evaporó con tolueno (3 veces 200 ml cada una) y se utilizó sin necesidad de purificación posterior en el siguiente paso. MS $^{m}/_{z}$: 186 (M+1).

(b) Etil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

Etóxido de sodio (1240.7 g de una solución de 21% en peso en EtOH, 3829 mmol) se agregó a una suspensión agitada de 2-cianoacetamida (298 g, 3544 mmol) en EtOH (3000 mL) durante 8 minutos bajo una atmósfera de nitrógeno a temperatura de la sala El producto de condensación crudo del paso (a) de arriba disuelto en 950 ml EtOH se agregó lentamente (reacción ligeramente exotérmica) y luego de haberse agregado alrededor de 1/3 se agregó más EtOH (1000 mL) para permitir una agitación eficiente (suspensión), seguida por la adición del resto del producto de condensación (tiempo de adición total 30 minutos). Luego de agitar de un día para otro a temperatura de la sala, se agregó HOAc (526 g, 8759 mmol) a la reacción y la mezcla se concentró *in vacuo* dejando una mezcla (***"a slurry"***) anaranjada espesa (volumen alrededor de 3000 mL), 1 M HCl (4628 mL, 4628 mmol) se agregó durante 10 minutos, seguido por agua (500 mL). Se detuvo la agitación y el precipitado se extrajo completamente por filtración y se lavó con agua (200 mL). NMR indicó la presencia de alrededor de 5-10% del ácido correspondiente, y el sólido se lavó agitando con más agua (1500 mL + 3 x 1000 mL), una solución de $NaHCO_3$ saturado (400 mL) en agua (600 mL) y, finalmente, agua (1000 mL). La filtración del sólido y el secamiento *in vacuo* a 80 °C produjeron etil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato puro. Rendimiento: 493 g (67%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.36 (3H, t, J = 7.1 Hz), 2.62 (3H, s), 4.25 (2H, q, J = 7.1 Hz), 8.71 (1H, s), 12.79 (1H, br s).

(c) Etil 6-cloro-5-ciano-2-metilnicotinato

Tolueno (4000 mL) y cloruro de tionilo (507 g, 4262 mmol) se agregaron a etil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (293 g, 1421 mmol) bajo una atmósfera de nitrógeno y la mezcla se calentó a 50 °C (temperatura del baño de aceite) y DMF (100 g, 1368 mmol) se agregó durante 2 minutos. La temperatura se aumentó a 80°C (temperatura del

baño de aceite) y la agitación se continuó durante 2 horas. La mezcla se concentró *in vacuo* (alrededor de 3.500 ml se evaporaron completamente) dejando un aceite rojo. EtOH (1000 mL, 99%) se agregó y luego se evaporó completamente. Se agregó diclorometano (4000 mL), seguido por solución $NaHCO_3$ al 4% (4000 mL) y la mezcla se agitó durante 15 minutos. La fase orgánica se separó y se evaporó para producir etil 6-cloro-5-ciano-2-metilnicotinato como un sólido crudo rojo oscuro, el cual se utilizó sin purificación adicional. Rendimiento: 301 g (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, J = 7.1 Hz), 2.91 (3H, s), 4.40 (2H, q, J = 7.1 Hz), 8.49 (1H, s).

(d) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico

Etil 6-cloro-5-ciano-2-metilnicotinato (50.98 g, 227 mmol), ácido azetidin-3-carboxílico (24.09 g, 238 mmol) y DIPEA (118.9 mL, 681 mmol) se suspendieron en EtOH (250 mL) y se calentaron a reflujo durante 1 hora. La mezcla de reacción se enfrió a temperatura de la sala y se agregó gota a gota a $KHSO_4$ (154.5 g, 1135 mmol) en agua (3000 mL). Los sólidos se recogieron por filtración y se secaron bajo vacío para proporcionar ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 65.33 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.72 (3H, s), 3.59-3.68 (1H, m), 4.31 (2H, q, J = 7.1 Hz), 4.55-4.68 (4H, m), 8.28 (1H, s).

MS $^m/_z$: 290 (M+1).

(e) Etil éster de ácido 5-ciano-6-[3-(2-metoxicarbonil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-1-metil-nicotínico

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.072 g, 0.25 mmol), metil 2-[(aminosulfonil)metil]benzoato

(0.085 g, 0.375 mmol) y trietilamina (0.55 mL, 4 mmol) se agitaron en DMF (2 mL). Se agregó HATU (0.100 g, 0.263 mmol) disuelto en DMF (1 mL) y la reacción se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se purificó mediante HPLC preparativa usando una columna 100x21.2mm Kromasil C8, partículas 5µ, Eluyente A: 100% acetonitrilo, Eluyente B: 95% 0,1M acetato de amonio/5% acetonitrilo, caudal 30 mL / min, gradiente 25% A a 75% A en 8 minutos para proporcionar etil éster de ácido 5-ciano-6-[3-(2-metoxicarbonil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico como un sólido. Rendimiento: 0.063 g (50%).

^{1}H NMR (400 MHz, DMSO-d_6) 1.26 (t, J = 7.2 Hz, 3H), 2.59 (s, 3H), 3.30 (m, 1H superpuesto por agua), 3.76 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 4.27 (t, J = 2.6 Hz, 2H), 4.35 (t, J = 4.3 Hz, 2H), 5.12 (s, 2H), 7.40 (d, J = 7.3 Hz, 1H), 7.48 (t, J = 3.9 Hz, 1H), 7.55 (t, J = 7.1 Hz, 1H), 7.78 (d, J = 7.7 Hz, 1H), 8.26 (s, 1H). MS $^m/_z$: 501 (M+1).

Ejemplo 2

Etil éster de ácido 6-[3-({[(3-bromobencil)sulfonil]amino}carbonil) azetidin-1-il]-5-ciano-2-metilnicotínico

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.257 g, 0.89 mmol), 1-(3-bromofenil)metanosulfonamida (0.223 g, 0.89 mmol) y TEA (0.360 g, 3.6 mmol) se agitaron en DMF (5 mL). Se agregó HATU (0.405 g, 1.07 mmol) y la mezcla de reacción se

realizó por HPLC preparativa (Kromasil C8 10µm 250 mm x 50 id. Eluyente A: 100% acetonitrilo, Eluyente B: 95% 0.1M acetato de amonio acuoso y acetonitrilo al 5%. Condiciones empleadas: Caudal 50 mL / minuto, se utilizó una gradiente lineal de 0% A a 100% A durante 42 minutos). El producto se precipitó durante la evaporación del disolvente y se extrajo completamente por filtración y se lavó con agua. Esto proporcionó el producto puro como un sólido blanco. Rendimiento: 0.181 g (39%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (t, J = 7.0 Hz, 3H), 2.62 (s, 3H), 3.56 (m, 1H), 4.23 (q, J = 7.0 Hz, 2H), 4.25-4.31 (m, 2H), 4.41 (m, 2H), 4.78 (s, 2H), 7.34 (m, 2H), 7.53 (s, 1H), 7.56-7.62 (m, 1H), 8.30 (s, 1H), 11.88 (s, 1H). MS $^m/_z$: 522 (M+1).

Ejemplo 3

Etil éster de ácido 5-ciano-2-metil-6-[3-(2-nitro-fenilmetanosulfonilaminocarbonil)azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 1-(2-nitrofenil) metanosulfonamida (0.111 g cruda, 0.37 mmol). Rendimiento: 0.031 g (25%).

^{1}H NMR (400 MHz, DMSO d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.5 (m, 1H, superpuesto por agua), 4.18 (q, J = 7.1 Hz, 2H), 4.26 (t, J = 3.1 Hz, 2H), 4.34 (t, J = 4.2 Hz, 2H), 5.04 (s, 2H), 7.51 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.3 Hz, 1H), 7.66 (t, J = 6.9 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 8.24 (s, 1H). MS $^m/_z$: 488 (M+1).

Ejemplo 4

Etil éster de ácido 6-[3-(2-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(2-clorofenil) metanosulfonamida (0.100 g cruda, 0.37 mmol). Rendimiento: 0.031 g (25%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.52 (m, 1H, superpuesto por agua), 4.18 (q, J = 7.1 Hz, 2H), 4.30 (t, J = 7.4 Hz, 2H), 4.40 (t, J = 9.4 Hz, 2H), 4.81 (s, 2H), 7.31 - 7.38 (m, 2H), 7.44 (m, 2H), 8.25 (s, 1H). MS $^m/_z$: 477 (M+1).

Ejemplo 5

Etil éster de ácido 6-[3-(4-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(4-clorofenil) metanosulfonamida (0.106 g cruda, 0.37 mmol). Rendimiento: 0.057 g (48%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.58 (s, 3H), 3.45 (m, 1H, superpuesto por agua), 4.18 (q, J = 7.1 Hz, 2H), 4.23 (m, 2H), 4.36 (t, J = 8.6 Hz, 2H), 4.65 (s, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 8.25 (s, 1H). MS $^m/_z$: 477 (M+1).

Ejemplo 6

Etil éster de ácido 5-ciano-2-metil-6-[3-(4-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 1-[4-(trifluorometil)fenil] metanosulfonamida (0.057g cruda, 0.23 mmol). Rendimiento: 0.050 g (39%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.49 (m, 1H, superpuesto por agua), 4.2 (q, J = 7.1 Hz, 2H), 4.24 (m, 2H), 4.36 (t, J = 8.8 Hz, 2H), 4.75 (s, 2H), 7.51 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 8.24 (s, 1H). MS $^m/_z$: 511 (M+1).

Ejemplo 7

Etil éster de ácido 5-ciano-6-[3-(3-fluoro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(3-fluorofenil) metanosulfonamida (0.095 g cruda, 0.37 mmol).Rendimiento: 0.065 g (56%).

^{1}H NMR (400 MHz, DMSO d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.48 (m, 1H, superpuesto por agua), 4.23 - 4.15 (m, 4H), 4.36 (t, J = 9.1 Hz, 2H), 4.69 (s, 2H), 7.18 - 7.09 (m, 3H), 7.36 (q, J = 7.5 Hz, 1H), 8.24 (s, 1H). MS $^m/_z$: 461 (M+1).

Ejemplo 8

Etil éster de ácido 5-ciano-2-metil-6-[3-(3-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 1-[3-(trifluorometil)fenil] metanosulfonamida (0.105 g cruda, 0.37 mmol). Rendimiento: 0.050 g (39%) .

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.48 (m, 1H), 4.18 (m, 4H), 4.35 (t, J = 8.8 Hz, 2H), 4.78 (s, 2H), 7.57 (m, 3H), 7.69 (d, J = 6.6 Hz, 1H), 8.24 (s, 1H). MS $^m/_z$: 511 (M+1).

Ejemplo 9

Etil éster de ácido 6-[3-(3-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(3-clorofenil) metanosulfonamida (0.096 g cruda, 0.37 mmol). Rendimiento: 0.050 g (42%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.46 (m, 1H superpuesto por agua), 4.23 - 4.15 (m, 4H), 4.35 (d, J = 9.3 Hz, 2H), 4.68 (s, 2H), 7.24 (d, J =7.3 Hz, 1H), 7.38 - 7.31 (m, 3H), 8.24 (s, 1H). MS $^m/_z$: 477 (M+1).

Ejemplo 10

Etil éster de ácido 6-{3-[2-(3-cloro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-5-ciano-2-metil-nicotínico

Preparado de acuerdo con el método A usando 2-(3-clorofenil) etanosulfonamida (0.102 g cruda, 0.37 mmol). Rendimiento: 0.055 g (45%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 2.98 (t, J = 7.5 Hz, 2H), 3.45 (m, 2H), 3.8-3.5 (m, 2H superpuesto por agua), 4.17 (m, 3H), 4.34 (t, J = 8.5 Hz, 2H), 7.17 (d, J = 7.1 Hz, 2H), 7.29 - 7.24 (m, 2H), 8.23 (s, 1H). MS $^m/_z$: 491 (M+1).

Ejemplo 11

Etil éster de ácido 5-ciano-2-metil-6-[3-(4-nitro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 1-(4-nitrofenil) metanosulfonamida (0.099 g cruda, 0.37 mmol). Rendimiento: 0.032 g (26%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.24 (t, J = 7.2 Hz, 3H), 2.56 (s, 3H), 3.44 (m, 1H), 4.18 (m, 4H), 4.33 (t, J = 8.4 Hz, 2H), 4.79 (s, 2H), 7.56 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 8.7 Hz, 2H), 8.23 (s, 1H). MS $^m/_z$: 488 (M+1)

Ejemplo 12

Etil éster de ácido 5-ciano-2-metil-6-[3-(2-fenil-etanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 2-feniletanosulfonamida (0.078 g cruda, 0.37).Rendimiento: 0.044 g (39%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.55 (s, 3H), 2.95 (t, J = 7.7 Hz, 2H), 3.45 (m, 1H), 4.17 (q, J = 7.1 Hz, 4H), 4.34 (t, J = 8.6 Hz, 2H), 7.25-7.12 (m, 5H), 8.23 (s, 1H). (Los dos protones próximos a la sulfona se traslapan con la señal DMSO). MS $^m/_z$: 457 (M+1)

Ejemplo 13

Etil éster de ácido 5-ciano-2-metil-6-(3-o-tolilmetanosulfonil aminocarbonil-azetidin-1-il)-nicotínico

Preparado de acuerdo con el método A usando 1-(2-metilfenil) metanosulfonamida (0.010 g cruda, 0.05mmol).Rendimiento: 0.002 g (2%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.2 Hz, 3H), 2.32 (s, 3H), 2.57 (s, 3H), 3.4 (m, 1H superpuesto por agua), 4.18 (m, 2H), 4.30 (m, 2H), 4.39 (m, 2H), 4.63 (s, 2H), 7.15 (m, 4H), 8.24 (s, 1H). MS $^m/_z$: 457 (M+1)

Ejemplo 14

Etil éster de ácido 5-ciano-2-metil-6-[3-(3-nitro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 1-(3-nitrofenil) metanosulfonamida (0.097 g cruda, 0.37 mmol). Rendimiento: 0.055 g (45%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 12 Hz, 3H), 2.57 (s, 3H), 3.46 (m, 1H), 4.18 (m, 4H), 4.32 (t, J = 9.2 Hz, 2H), 4.82 (s, 2H), 7.63 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 8.10 (s, 1H), 8.17 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H). MS $^m/_z$: 488 (M+1).

Ejemplo 15

Etil éster de ácido 5-ciano-6-{3-[2-(4-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico

Preparado de acuerdo con el método A usando 2-(4-fluorofenil) etanosulfonamida (0.082 g cruda, 0.37 mmol). Rendimiento: 0.051 g (43%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.55 (s, 3H), 2.95 (t, J = 7.6 Hz, 2H), 3.48 (m, 1H), 3.70 - 3.50 (m, 2H), 4.17 (q, J = 7.2 Hz, 4H), 4.36 (t, J = 9.0 Hz, 2H), 7.04 (t, J = 8.9 Hz, 2H), 7.24 (dd, J = 8.6, 5.5 Hz, 2H), 8.23 (s, 1H). MS $^m/_z$: 475 (M+1).

Ejemplo 16

Etil éster de ácido 5-ciano-2-metil-6-[3-(2-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico

Preparado de acuerdo con el método A usando 1-[2-(trifluorometil)fenil] metanosulfonamida (0.100 g cruda, 0.37 mmol). Rendimiento: 0.045 g (35%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.58 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.31 (t, J = 6.9 Hz, 2H), 4.41 (t, J = 8.8 Hz, 2H), 4.83 (s, 2H), 7.68 - 7.54 (m, 3H), 7.74 (d, J = 8.1 Hz, 1H), 8.24 (s, 1H). MS $^m/_z$: 511 (M+1).

Ejemplo 17

Etil éster de ácido 5-ciano-6-[3-(4-fluoro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(4-fluorofenil) metanosulfonamida (0.078 g cruda, 0.37 mmol). Rendimiento: 0.050 g (43%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.24 (t, J = 7.1 Hz, 3H), 2.57 (s, 3H), 3.49 (m, 1H), 4.20 (m, 4H), 4.36 (t, J = 9.0 Hz, 2H), 4.65 (s, 2H), 7.13 (t, J = 8.8 Hz, 2H), 7.32 (dd, J = 8.6, 5.5 Hz, 2H), 8.25 (s, 1H). MS $^m/_z$: 461 (M+1).

Ejemplo 18

Etil éster de ácido 5-ciano-6-(3-ciclopentilmetanosulfonil aminocarbonil-azetidin-1-il)-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-ciclopentilmetanosulfonamida (0.074 g cruda, 0.37 mmol). Rendimiento: 0.013 g (12%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.21 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.44 (m, 2H), 1.52 (m, 2H), 1.79 (m, 2H), 2.13 (m, 1H), 2.56 (s, 3H), 3.38 (d, J = 6.8 Hz, 2H), 3.51 (m, 1H superpuesto por agua), 4.17 (q, J = 7.1 Hz,

2H), 4.29 (m, 2H), 4.41 (t, J = 9.0 Hz, 2H), 8.23 (s, 1H). MS $^{m}/_{z}$: 435.0 (M+1).

Ejemplo 19

Etil éster de ácido 5-ciano-6-{3-[2-(2-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico

Preparado de acuerdo con el método A usando 2-(2-fluorofenil) etanosulfonamida (0.084 g cruda, 0.37 mmol). Rendimiento: 0.060 g (51%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 2.99 (t, J = 7.7Hz, 2H), 3.46 (m, 1H superpuesto por agua), 3.67 - 3.54 (m, 2H superpuesto por agua), 4.17 (m, 4H), 4.36 (t, J = 8.8 Hz, 2H), 7.08 (t, J = 8.0 Hz, 2H), 7.21 (m, 1H), 7.30 (t, J = 7.7 Hz, 1H), 8.23 (s, 1H). MS $^{m}/_{z}$: 475 (M+1).

Ejemplo 20

Etil éster de ácido 5-ciano-6-[3-(3,5-dicloro-fenilmetanosulfonil aminocarbonil)-azetidin-1-il]-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(3,5-diclorofenil) metanosulfonamida (0.181 g cruda, 0.37 mmol). Rendimiento: 0.053 g (41%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.56 (s, 3H), 3.47 (m, 1H), 4.18 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.35 (t, J = 9 Hz, 2H), 4.69 (s, 2H), 7.30 (s, 2H), 7.55 (s, 1H), 8.23 (s, 1H). MS $^{m}/_{z}$: 511 (M+1).

Ejemplo 21

Etil éster de ácido 5-ciano-6-(3-ciclohexilmetanosulfonilaminocarbonil-azetidin-1-il)-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-ciclohexilmetanosulfonamida (0.065 g cruda, 0.37 mmol). Rendimiento: 0.012 g (11%).

^{1}H NMR (400 MHz, DMSO-d_6) d 0.98-1.25 (m, 8H), 1.60 - 1.50 (m, 3H), 1.74 (m, 3H), 2.55 (s, 3H), 3.26 (d, J = 6.0 Hz, 2H), 3.58 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.28 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 8.7 Hz, 2H), 8.23 (s, 1H). MS $^m/_z$: 449 (M+1).

Ejemplo 22

Etil éster de ácido 5-ciano-6-{3-[2-(3-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico

Preparado de acuerdo con el método A usando 2-(3-fluorofenil) etanosulfonamida (0.088 g cruda, 0.37 mmol). Rendimiento: 0.044 g (37%). ^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.56 (s, 3H), 2.98 (t, J = 7.7 Hz, 2H), 3.45 (m, 1H traslapado por agua), 3.69 - 3.56 (m, 2H traslapado por agua), 4.17 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 4.35 (t, J = 8.9 Hz, 2H), 6.95 (m, 1H), 7.06 (m, 2H), 7.27 (dd, J = 14.4, 8.0 Hz, 1H), 8.23 (s, 1H). MS $^m/_z$: 475 (M+1).

Ejemplo 23

Etil éster de ácido 6-[3-(benzo[d]isoxazol-3-ilmetanosulfonil aminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico

Preparado de acuerdo con el método A usando 1-(1,2-benzisoxazol-3-il) metanosulfonamida (0.080 g, 0.37 mmol). Rendimiento: 0.035 g (28%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.26 (t, J = 7.1 Hz, 3H), 2.58 (s, 3H), 3.27 (m, 1H superpuesto por agua), 4.20 (q, J = 7.1 Hz, 2H), 4.84 (s, 2H), 4.27 (m, 4H), 7.28 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 8.24 (s, 1H). MS $^m/_z$: 484 (M+1).

Ejemplo 24

1-[4-Amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]-*N*-(bencilsulfonil)piperidin-4-carboxamida

(a) 5,6-Dicloro-N-(2-hidroxibutil)nicotinamida

Ácido 5,6-dicloronicotínico (20.0 g, 104 mmol), EDCI (26.0 g, 135 mmol) y HOBt (18.3 g, 135 mmol) se disolvieron en DCM (500 mL) a temperatura de la sala. La mezcla de reacción se agitó a temperatura de la sala durante 90 minutos y luego se agregaron 1-aminobutan-2-ol (15.0 g, 156 mmol) y DIPEA (54.4 mL, 313 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con DCM (400 mL) y los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 100 mL), $NaHCO_3$ saturado (2 x 100 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar 5,6-dicloro-N-(2-hidroxibutil)nicotinamida como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(b) 5,6-Dicloro-N-(2-oxobutil)nicotinamida

Cloruro de oxalilo (16.3 mL, 187 mmol) se disolvió en DCM (500 mL) y se enfrió a -78 °C. Se agregó DMSO (26.3 mL, 374 mmol) gota a gota y se agitó a -78 °C durante 10 minutos. 5,6-Dicloro-N-(2-hidroxibutil) nicotinamida (30 g, 94 mmol) se disolvió en DCM / DMSO (3:1) y se agregó lentamente a la solución. La solución se agitó a -78 °C durante 30 minutos. Se agregó TEA (65.2 mL, 467 mmol) a la solución y se agitó durante 30 minutos. La solución se calentó a temperatura de la sala y se agitó durante 3 horas. La mezcla de reacción se diluyó con DCM (200 mL) y los orgánicos combinados se lavaron con agua (2 x 200 mL), salmuera (2 x 200 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar 5,6-dicloro-N-(2-oxobutil)nicotinamida como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(c) 2,3-Dicloro-5-(5-etil-1,3-oxazol-2-il)piridina

5,6-Dicloro-N-(2-oxobutil)nicotinamida (26.7 g, 78 mmol) y $POCl_3$ (59.6 g, 389 mmol) se disolvieron en DMF (500 mL) y se calentaron a 90°C durante 30 minutos. La mezcla de reacción se virtió en hielo. Se agregó $NaHCO_3$ sólido en porciones hasta que el pH se elevó a pH > 8. La mezcla de reacción se diluyó con agua (500 mL) y los acuosos combinados se lavaron

con EtOAc (3 x 400 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (EtOAc/hexanos, 1/9) produjo 2,3-dicloro-5-(5-etil-1,3-oxazol-2-il)piridina como un sólido. Rendimiento: 7.08 g (37.5%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (2H, t, J = 7.5 Hz), 2.78 (2H, q, J = 7.5 Hz), 6.91 (1H, s), 8.35 (1H, d, J = 1.9 Hz) 8.29 (1H, d, J = 1.9 Hz).
MS $^m/_z$: 244 (M+1).

(d) 2,3-Dicloro-5-(5-etil-1,3-oxazol-2-il)-4-(metiltio)piridina

n-Butil litio (2.5 M en hexanos, 7.14 mL, 17 mmol) se agregó gota a gota a diisopropilamina (2.62 mL, 19 mmol) en THF (5 mL) a 0 °C. La solución se agitó a 0 °C durante 30 minutos y luego se enfrió a -78 °C. Se agregó 2,3-dicloro-5-(5-etil-1,3-oxazol-2-il)piridina (3.50 g, 14 mmol) en THF (30 mL) a la solución y la reacción se agitó a -78 °C durante 1 hora. Se agregó S-metil metanosulfonotioato (1.77 mL, 19 mmol) y la solución se calentó a temperatura de la sala. La mezcla de reacción se agitó durante 16 horas. La mezcla de reacción se diluyó con NH_4Cl saturado (100 mL). La solución se lavó con EtOAc (3 x 50 mL). Los orgánicos combinados se lavaron con salmuera (1 x 50 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (15% EtOAc/hexanos a 20% EtOAc/hexanos) produjo 2,3-dicloro-5-(5-etil-1,3-oxazol-2-il)-4-(metiltio)piridina como un sólido. Rendimiento: 2.71 g (65.1%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (2H, t, J = 7.6 Hz), 2.35 (3H, s), 2.79 (2H, q, J = 7.6 Hz), 6.98 (1H, s), 8.58 (1H, s). MS $^m/_z$: 290 (M+1).

(e) Metil 1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)-4-(metiltio)piridin-2-il] piperidin-4-carboxilato

2,3-Dicloro-5-(5-etil-1,3-oxazol-2-il)-4-(metiltio)piridina (3.11 g, 11 mmol), metil piperidin-4-carboxilato (2.00 g, 14 mmol) y DIPEA (3.75 mL, 22 mmol) se disolvieron en DMA (50 mL) y se calentaron a 120 °C durante 2 horas. La mezcla de reacción se enfrió a temperatura de la sala y se

concentró bajo presión reducida. El material crudo se disolvió en EtOAc (100 mL), se lavó con NH_4Cl (2 x 60 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (1:5 EtOAc/hexanos a 1:3 EtOAc/hexanos) produjo metil 1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)-4-(metiltio)piridin-2-il] piperidin-4-carboxilato como un sólido. Rendimiento: 4.26 g (87.6%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (2H, t, J = 7.6 Hz), 1.88-2.06 (4H, m), 2.32 (3H, s), 2.51-2.58 (1H, m), 2.76 (3H, q, J = 7.6 Hz), 2.93-2.99 (2H, m), 3.72 (3H, s), 3.81-3.92 (2H, m), 6.91 (1H, s), 8.43 (1H, s). MS $^m/_z$: 396 (M+1).

(f) Metil 1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)-4-(metilsulfinil)piridin-2-il]piperidin-4-carboxilato

Metil 1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)-4-(metiltio)piridin-2-il]piperidin-4-carboxilato (2.12 g, 5.4 mmol) se disolvió en DMF (500 mL) y se agregó ácido 3-clorobencenocarboperoxoico (2.64 g, 10.7 mmol) lentamente a temperatura de la sala. La solución se agitó a temperatura de la sala durante 4 horas. Se agregó ácido 3-clorobencenocarboperoxoico (1.32 g, 5.35 mmol) lentamente a temperatura de la sala durante 3 horas. Se agregó $Na_2S_2O_3$ (30 mL) saturado y la solución se agitó durante 5 minutos. La mezcla de reacción se diluyó con CH_2Cl_2 (40 mL) y los orgánicos combinados se separaron y se lavaron con NaOH (1M, 2 x 40 mL), salmuera (1 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (1:2 EtOAc/hexanos) produjo metil 1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)-4-(metilsulfinil)piridin-2-il]piperidin-4-carboxilato como un sólido. Rendimiento: 2.71 g (65.1%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (1H, t, J = 7.5 Hz), 1.83-2.08 (4H, m) 2.52-2.61 (1H, m), 2.75 (2H, q, J = 7.5Hz), 2.93-3.00 (1H, m), 3.04-3.13 (1H, m), 3.23 (3H, s), 3.72 (3H, s), 3.86-4.01 (2H, m), 6.87 (1H, s), 8.51 (1H, s). MS $^m/_z$: 412 (M+1).

(g) Metil 1-[4-azido-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxilato

Metil 1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)-4-(metilsulfinil)piridin-2-il]piperidin-4-carboxilato (0.150 g, 0.36 mmol) y azida de sodio (0.026 g, 0.40 mmol) se disolvieron en DMA (1 mL) y se agitaron a temperatura de la sala durante 48 horas. La mezcla de reacción se diluyó con EtOAc (40 mL) y los orgánicos combinados se separaron se lavaron con agua (2 x 40 mL), salmuera (1 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar metil 1-[4-azido-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]piperidin-4-carboxilato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(h) Metil 1-[4-amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxilato

Metil 1-[4-azido-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]piperidin-4-carboxilato (0.150 g, 0.36 mmol) se disolvió en THF (0.90 mL) y se enfrió a 0 °C. Se agregó polvo de zinc (0.109 g, 1.66 mmol). Se agregó NH_4Cl (0.900 mL) lentamente a la solución. La solución se calentó a temperatura de la sala durante 1.5 horas. La mezcla de reacción se filtró (celita) y se diluyó con EtOAc (40 mL) y los orgánicos combinados se lavaron con NH_4OAc saturado (2 x 30 mL), salmuera (1 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar metil 1-[4-amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]piperidin-4-carboxilato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(i) Ácido 1-[4-amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxílico

Metil 1-[4-amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxilato-(0.045 g, 0.123 mmol), e hidróxido de litio (2 M, 1.23 mL, 2.46 mmol) se suspendieron en THF (1 mL) y se agitaron a temperatura de la sala durante 16 horas. Se agregó HCl (concentrado) gota a gota a la mezcla

de la sala durante 16 horas. Yodoetano (0.670 mL, 6.60 mmol) y carbonato de potasio (3.90 g, 28.25 mmol) se agregaron a la mezcla de reacción y se agitaron a temperatura de la sala durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 mL) y los orgánicos combinados se lavaron con agua (2 x 40 mL), salmuera (1 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar etil 4-azido-5,6-dicloronicotinato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(b) Etil 4-amino-5,6-dicloronicotinato

Etil 4-azido-5,6-dicloronicotinato (0.700 g, 2.68 mmol) se disolvió en 1:1 THF/MeOH (10 mL). Se agregó polvo de zinc (0.109 g, 1.66 mmol) y la solución se enfrió a 5°C. NH_4Cl (2 mL) se agregó lentamente a la solución. La solución se calentó a temperatura de la sala durante 2 horas. La mezcla de reacción se filtró (celita), se lavó con MeOH (50 mL) y se concentró para proporcionar etil 4-amino-5,6-dicloronicotinato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(c) Ácido 1-[4-amino-3-cloro-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico

Ácido etil 4-amino-5,6-diclórico (0.320 g, 1.36 mmol), ácido piperidin-4-carboxílico (0.352 g, 2.72 mmol) y DIPEA (11.9 mL, 68.2 mmol) se disolvieron en DMA (2.5 mL) y se calentaron a 120°C durante 2 horas. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. El material crudo se disolvió en EtOAc (40 mL), se lavó con NH_4Cl (1 x 40 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (EtOAc/hexanos 1/3 a EtOAc/hexanos 2/3 con 0.5% AcOH) produjo ácido 1-[4-amino-3-cloro-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico como un sólido. Rendimiento: 0.154 g (34.5%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (2H, t, J = 7.1 Hz), 1.88-2.07 (4H, m), 2.55-2.62 (1H, m), 2.92-3.01 (2H, m), 3.87-3.90 (2H, m), 4.33 (3H, q, J = 7.1 Hz), 8.60 (1H, s). MS $^m/_z$: 328 (M+1).

(d) Etil éster de ácido 4-amino-6-(4-{[(bencilsulfonil)amino]carbonil} piperidin-1-il)-5-cloronicótico

Ácido 1-[4-amino-3-cloro-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico (0.070 g, 0.21 mmol), EDCI (0.053 g, 0.28 mmol) y HOBt (0.038 g, 0.28 mmol) se disolvieron en DCM (5 mL) a temperatura de la sala. La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos y luego se agregaron 1-fenilmetanosulfonamida (0.051 g, 0.30 mmol) y DIPEA (0.22 mL, 1.3 mmol). La mezcla de reacción se agitó a temperatura de la sala hasta que se observó un consumo completo del material inicial por Análisis HPLC. La mezcla de reacción se diluyó con DCM (30 mL) y se lavó con NH_4Cl saturado (2 x 30 mL). Los orgánicos combinados se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (3:7 EtOAc/hexanos, luego 3:7 EtOAc/hexanos con 0.5% AcOH) produjo etil éster de ácido 4-amino-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloronicótico como un sólido. Rendimiento: 0.079 g (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.4 Hz), 1.83-1.88 (4H, m), 2.28-2.36 (1H, m), 2.81-2.88 (2H, m), 3.92-3.95 (2H, m), 4.33 (2H, q, J = 7.4 Hz), 4.69 (4H, s), 7.35-7.41 (5H, m), 8.59 (1H, s). MS $^m/_z$: 481 (M+1).

Ejemplo 26

Isopropil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicotínico

(a) Ácido 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotínico

Etil 6-(3-(*terc*-butoxicarbonil)azetidin-1-il)-5-ciano-2-metilnicotinato (1.50 g, 4.16 mmol), e hidróxido de litio (3.00 g, 8.32 mmol) se suspendieron en

MeOH (40 mL) y se calentaron a 90 °C durante 1 h. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. El precipitado se filtró y se recogió. El licor madre se lavó con EtOAc (1 x 60 mL), se secó ($MgSO_4$), se concentró bajo presión reducida y se combinó con el sólido para proporcionar ácido 6-{3-[(*terc*-butoxicarbonil)amino] azetidin-1-il}-5-ciano-2-metilnicotínico como un sólido, el cual se utilizó crudo.

(b) Isopropil 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotinato

Ácido 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotínico (0.400 g, 1.20 mmol), 2-yodopropano (0.181 mL, 1.81 mmol), y carbonato de potasio (0.216 g, 1.56 mmol) se disolvieron en DMA (5 mL). La mezcla de reacción se agitó a temperatura de la sala durante 16 horas. Se agregó 2-yodopropano (0.154 g, 0.91 mmol) a la solución y se continuó la agitación durante 8 horas más. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con $NaHCO_3$ saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar isopropil 6-{3-[(*terc*-butoxicarbonil)amino] azetidin-1-il}-5-ciano-2-metilnicotinato como un sólido, el cual se utilizó crudo.

(c) Isopropil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato bis (trifluoroacetato)

Isopropil 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotinato (0.376 g, 1.00 mmol) se disolvió en DCM (1 mL). Se agregó lentamente TFA (1.16 mL, 15.1 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 16 horas. La mezcla se concentró bajo presión reducida para proporcionar isopropil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato bis(trifluoroacetato) como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(d) Isopropil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil} amino)azetidin-1-il]-5-ciano-2-metilnicotínico

1,1'-Carbonilbis(1H-imidazol) (0.035 g, 0.216 mmol) y 1-fenilmetanosulfonamida (0.037 g, 0.216 mmol) se disolvieron en DCE (2 mL) y se agitaron durante 16 horas a temperatura de la sala. Isopropil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato bis(trifluoroacetato) (0.102 g, 0.216 mmol) en DCE (2 mL) y DIPEA (0.564 mL, 0.740 mmol) se agregaron a la mezcla de reacción y la agitación se agitó a temperatura de la sala durante 16 horas. La mezcla de reacción se calentó a 70 °C durante 16 horas. 1,1'-Carbonilbis(1H-imidazol) (0.035 g, 0.216 mmol) y 1-fenilmetanosulfonamida (0.037 g, 0.216 mmol) se agregaron a la solución y la mezcla de reacción se calentó a 70 °C durante 16 horas. La mezcla de reacción se concentró bajo presión reducida y se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con $NaHCO_3$ saturado (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. La trituración (1:1 EtOAc/hexanos) produjo isopropil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil} amino)azetidin-1-il]-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.017 g (16.2%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (6H, d, J = 6.2 Hz), 2.62 (3H, s), 4.18 (2H, m), 4.55 (3H, m), 4.69 (2H, m), 5.03-5.09 (1H, m), 7.10 (1H, s), 7.32-7.40 (5H, m), 8.31 (1H, s), 10.5 (s, 1H). MS $^m/_z$: 472 (M+1).

Ejemplo 27

***terc*-Butil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicotínico**

(a) Ácido *terc*-butil 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotínico

Ácido 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotínico (0.400 g, 1.20 mmol), y *terc*-butil imidocarbamato (0.964 g, 4.80 mmol) se disolvieron en THF (5. mL) y se calentaron a 80°C durante 27 horas. La mezcla de reacción se concentró bajo presión reducida. La

mezcla de reacción se diluyó con DCM (40 mL) y se filtró a través de un tapón de sílice con EtOAc. El filtrado se concentró bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (1:6 EtOAc/hexanos) produjo ácido *terc*-butil 6-{3-[(*terc*-butoxicarbonil)amino] azetidin-1-il}-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.342 g (73.2%).

(b) Diclorhidrato de *terc*-butil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato

Ácido *terc*-butil 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotínico (0.342 g. 0.880 mmol) se disolvió HCl (1 M en dioxano, 4.40 mL, 4.40 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 16 horas y se concentró bajo presión reducida para producir diclorhidrato de *terc*-butil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(c) *terc*-Butil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil} amino)azetidin-1-il]-5-ciano-2-metilnicotínico

1,1'-Carbonilbis(1H-imidazol) (0.034 g, 0.208 mmol) y 1-fenilmetanosulfonamida (0.034 g, 0.208 mmol) se disolvieron en DCE (2 mL) y se agitaron durante 16 horas a temperatura de la sala. Diclorhidrato de *terc*-butil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato (0.130 g, 0.208 mmol) en DCE (2 mL) y DIPEA (2.08 mL, 0.362 mmol) se agregaron a esta solución y se agitaron a temperatura de la sala durante 48 horas. La mezcla de reacción se calentó a 70°C durante 16 horas. La mezcla de reacción se concentró bajo presión reducida y se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con $NaHCO_3$ saturado (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (1:6 EtOAc/hexanos), seguida por trituración (1:1 EtOAc/hexanos) produjo *terc*-butil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino)

azetidin-1-il]-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.031 g (30%).

^{1}H NMR (400 MHż, DMSO-d_6): δ 1.52 (9H, s), 2.60 (3H, s), 4.16 (2H, m), 4.55 (3H, m), 4.69 (2H, m), 7.10 (1H, s), 7.33-7.40 (5H, m), 8.23 (1H, s), 10.5 (1H, s). MS $^m/_z$: 486 (M+1).

Ejemplo 28

Etil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicótico

(a) Etil 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotinato

Etil 6-cloro-5-ciano-2-metilnicotinato (6.20 g, 29.4 mmol), *terc*-butil azetidin-3-ilcarbamato (5.07 g, 29.4 mmol), y DIPEA (5.13 mL, 29.4 mmol) se disolvieron en DCE (40 mL) y se agitaron a temperatura de la sala durante 1 hora. La mezcla de reacción se concentró bajo presión reducida y se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con $NaHCO_3$ saturado (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (1:6 EtOAc/hexanos) produjo etil 6-{3-[(*terc*-butoxicarbonil) amino]azetidin-1-il}-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 7.00 g (66.0%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.2 Hz), 1.46 (9H, s), 2.70 (1H, s), 4.18-4.22 (2H, m), 4.30 (2H, q, J = 7.2 Hz), 4.59 (1H, s), 4.67-4.72 (2H, m), 5.00 (1H, s), 8.26 (1H, s).

MS $^m/_z$: 361 (M+1).

(b) Etil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato bis (trifluoroacetato)

Etil 6-{3-[(*terc*-butoxicarbonil)amino]azetidin-1-il}-5-ciano-2-metilnicotinato (1.00 g, 2.77 mmol) se disolvió en DCM (10 mL). TFA (6.40 mL, 83.2 mmol) se agregó lentamente. La mezcla de reacción se agitó

a temperatura de la sala durante 30 minutos. La mezcla se concentró bajo presión reducida para proporcionar etil 6-(3-aminoazetidin-1-il)-5-ciano-2-metilnicotinato bis(trifluoroacetato) como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

(c) Etil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicótico

1,1'-Carbonilbis(1H-imidazol) (0.054 g, 0.333 mmol) y 1-fenil metanosulfonamida (0.057 g, 0.333 mmol) se disolvieron en DCE (2 mL) y se agitaron durante 16 horas a temperatura de la sala. 6-(3-Aminoazetidin-1-il)-5-ciano-2-metilnicotinato bis(trifluoroacetato) (0.210 g, 0.333 mmol) en DCE (2 mL) y DIPEA (0.580 mL, 3.33 mmol) se agregaron a esta solución y se agitaron a temperatura de la sala durante 2 horas. La mezcla de reacción se concentró bajo presión reducida y se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con $NaHCO_3$ saturado (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. La trituración (1:1 EtOAc/hexanos) produjo etil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicótico como un sólido. Rendimiento: 0.073 g (47.9%)

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, 1, J = 7.1 Hz), 2.63 (3H, s), 2.70 (1H, s), 4.18- 4.19 (2H, m), 4.24 (2H, q, J = 7.1 Hz), 4.56 (3H, m), 4.70 (2H, m), 7.1 (1H, s), 7.32-7.43 (5H, m), 8.31 (1H, s).

MS $^m/_z$: 458 (M+1).

Ejemplo 29

Etil éster de ácido 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}piperidin-1-il)-5-ciano-2-metilnicotínico

(a) Sal de potasio de ácido piperidin-3-ilacético

Trimetilsilanoato de potasio (0.89 g, 5.2 mmol) y etil piperidin-3-ilacetato (0.87 g, 6.8 mmol) se agitaron en DCM (50 mL) a temperatura de la sala

durante 2 días. La concentración de la mezcla de reacción proporcionó el ácido piperidin-3-ilacético como la sal de potasio, el cual se utilizó crudo asumiendo una conversión completa. Rendimiento: 0.74 g (100%).

(b) Ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-1-il]piperidin-3-il}acético

Etil 6-cloro-5-ciano-2-metilnicotinato (1.00 g, 4.45 mmol), ácido piperidin-3-ilacético (0.701 g, 4.90 mmol) y DIPEA (2.33 mL, 13:4 mmol) se disolvieron en DMF (30 mL) y se agitaron a temperatura de la sala durante 3 días. La mezcla de reacción se diluyó con EtOAc (100 mL), se lavó con NH_4Cl saturado (2 x 25 mL), $NaHCO_3$ saturado (2 x 25 mL), salmuera (25 m), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (9:1 EtOAc/hexanos con 1% HOAc) produjo ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-3-il}acético como un sólido. Rendimiento: 0.791 g (54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.39-1.44 (1H, m), 1.63-1.73 (1H, m), 1.78-1.85 (1H, m), 1.98-2.03 (1H, m), 2.16-2.24 (1H, m), 2.29-2.34 (1H, m), 2.40-2.46 (1H, m), 2.71 (3H, s), 3.08-3.13 (1H, m), 3.26-3.32 (1H, m), 4.31 (2H, q, J = 7.1 Hz), 4.44- 4.50 (1H, m), 4.52-4.56 (1H, m), 8.33 (1H, s).

MS $^m/_z$: 330 (M-1).

(c) Etil éster de ácido 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil} piperidin-1-il)-5-ciano-2-metilnicotínico

Ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-3-il} acético (0.152 g, 0.459 mmol), EDCI (0.114 g, 0.596 mmol), HOBt (0.081 g, 0.596 mmol), 1-fenilmetanosulfonamida (0.102 g, 0.596 mmol) y DIPEA (0.160 mL, 917 mmol) se disolvieron en DCM (6 mL) y se agitaron a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó con NH_4Cl (2 x 40 mL) saturado y salmuera (40 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión

reducida para proporcionar el producto crudo. Cromatografía instantánea (1:4 EtOAc/hexanos, 1.0% AcOH produjo etil éster de ácido 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}piperidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.065 g (28%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35-1.40 (3H, m), 1.53-1.58 (1H, m), 1.64-1.71 (1H, m), 1.73-1.80 (1H, m), 1.93-2.00 (1H, m), 2.11-2.22 (2H, m), 2.27-2.34 (1H, m), 2.68 (3H, s), 3.09-3.16 (1H, m), 3.30-3.38 (1H, m), 4.29-4.40 (4H, m), 4.68 (2H, s), 7.37-7.38 (5H, m), 7.70 (1H, br s), 8.33 (1H, s). MS $^m/_z$: 485 (M+1).

Ejemplo 30

Etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}-4-metilpiperidin-1-il)-5-ciano-2-metilnicotínico

(a) 1-*terc*-Butil 4-metil piperidin-1,4-dicarboxilato

Ácido 1-(*terc*-butoxicarbonil)piperidin-4-carboxílico (3.00 g, 13 mmol) se disolvió en MeOH (50 mL) y $TMSCHN_2$ (32.7 mL de una solución 2 M en hexanos, 65 mmol) se agregó gota a gota a temperatura de la sala. Se agregó $TMSCHN_2$ hasta que se produjo un color amarillo persistente, que indicaba el exceso de reactivo. AcOH se agregó gota a gota para extinguir el exceso de $TMSCHN_2$ y la mezcla de reacción se concentró bajo presión reducida y se destiló bajo una temperatura fija con tolueno (3 x 30 mL) para eliminar cualquier traza de MeOH o AcOH. El 1-*terc*-butil 4-metil piperidin-1,4-dicarboxilato crudo se utilizó sin purificación adicional.

(b) 1-*terc*-Butil 4-metil 4-metilpiperidin-1,4-dicarboxilato

DIPA (2.40 mL, 17 mmol) se disolvió en THF (60 mL) y se enfrió a 0 °C. Butil litio 1.6 M en hexanos (9.81 mL, 16 mmol) se agregó gota a gota y el sistema se agitó a 0 °C durante 1 hora. La mezcla de reacción se enfrió a -78 °C, y una solución de 1-*terc*-butil 4-metil piperidin-1,4-dicarboxilato (3.18 g, 13 mmol) en THF (30 mL) se agregó gota a gota durante 30 minutos. La mezcla de reacción se agitó a -78 °C durante 2 horas y luego se

agregó yodometano (1.31 mL, 21 mmol) en THF (10 mL) en una porción y la mezcla de reacción se agitó durante 2 horas. El sistema se dejó calentar a temperatura de la sala de un día para otro. La mezcla de reacción se extinguió con NH_4Cl saturado (100 mL) y se extrajo en EtOAc (100 mL). Los orgánicos combinados se lavaron con salmuera (70 mL) y se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el 1-*terc*-butil 4-metil 4-metilpiperidin-1,4-dicarboxilato crudo como un sólido, el cual se utilizó sin purificación adicional.

(c) Metil 4-metilpiperidin-4-carboxilato

1-*terc*-Butil 4-metil 4-metilpiperidin-1,4-dicarboxilato (3.37 g, 13.1 mmol) se suspendió en THF (15 mL) y se agregó 4 M HCl en 1,4-dioxano (65.4 mL, 262 mmol) y la mezcla de reacción se agitó a temperatura de la sala hasta que se observó el consumo completo del material de partida mediante análisis TLC. La mezcla de reacción se concentró bajo presión reducida para proporcionar el material crudo. Los sólidos se repartieron en porciones entre $NaHCO_3$ saturado y DCM.

Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. La purificación por cromatografía instantánea, (eluyente 0.5% TEA, 2% MeOH / DCM - 1% TEA, 5% MeOH / DCM) produjo metil 4-metilpiperidin-4-carboxilato como un aceite. Rendimiento: 0.910 g (44%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, s), 1.44-1.55 (2H, m), 2.09-2.20 (2H, m), 2.69-2.80 (2H, m), 2.98-3.08 (2H, m), 3.72 (3H, s), 3.99 (1H, br s). MS $^m/_z$: 158 (M+1).

(d) Clorhidrato de ácido 4-metilpiperidin-4-carboxílico

Metil 4-metilpiperidin-4-carboxilato (0.300 g, 1.9 mmol) se suspendió en THF (30 mL) y se agregó trimetilsilanolato de potasio (2.4 g, 19 mmol). El sistema se calentó a reflujo a reflujo de un día para otro y luego se enfrió a temperatura de la sala. Se agregó 4 M HCl en 1,4-dioxano (12 mL, 48 mmol) y el sistema se concentró bajo presión reducida para proporcionar

clorhidrato de ácido 4-metilpiperidin-4-carboxílico crudo como un sólido, el cual se utilizó sin purificación adicional.

(e) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]-4-metilpiperidin-4-carboxílico

Etil 6-cloro-5-ciano-2-metilnicotinato (0.28 g, 1.3 mmol) y clorhidrato de ácido 4-metilpiperidin-4-carboxílico (0.34 g, 1.9 mmol) se suspendieron en DMF (20 mL) y se agregó DIPEA (1.1 mL, 6.3 mmol). La mezcla de reacción se agitó hasta que se observó el consumo completo del material de partida por análisis HPLC. La mezcla de reacción se diluyó con EtOAc (100 mL) y se lavó con NH_4Cl (70 mL) saturado, agua (2 x 70 mL) y salmuera (50 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía en columna instantánea (1:3 EtOAc/hexanos, 0.5% AcOH a 1:2 EtOAc/hexanos, 0.5% AcOH) produjo ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]-4-metilpiperidin-4-carboxílico como un sólido.

Rendimiento: 0.179 g (43%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20 (3H, s), 1.30 (3H, t, J = 7.1Hz), 1.44-1.54 (2H, m), 2.02-2.11 (2H, m), 2.63 (3H, s), 3.39-3.48 (2H, m), 4.15-4.29 (4H, m), 8.32 (1H, s), 12.52 (1H, br s). MS $^m/_z$: 332 (M+1).

(f) Etil éster ácido 6-(4-{[(bencilsulfonil)amino]carbonil}-4-metilpiperidin-1-il)-5-ciano-2-metilnicotínico

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]-4-metilpiperidin-4-carboxílico (0.074 g, 0.22 mmol), EDCI (0.056 g, 0.29 mmol) y HOBt (0.039 g, 0.29 mmol) se disolvieron en DCM (10 mL) a temperatura de la sala. La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos y luego se agregaron1-fenilmetanosulfonamida (0.054 g, 0.31 mmol) y DIPEA (0.23 mL, 1.3 mmol). La mezcla de reacción se agitó a temperatura de la sala hasta que se observó un consumo completo del material inicial por análisis HPLC. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con NH_4Cl (20 mL) saturado. Los orgánicos se

secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (3:7 EtOAc/hexanos, 0.5% AcOH a 1:1 EtOAc/hexanos, 0.5% AcOH), seguida por HPLC preparativa produjo etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}-4-metilpiperidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.038 g (35%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (3H, s), 1.38 (3H, 1, *J* = 7.0 Hz), 1.54-1.62 (2H, m), 2.00-2.09 (2H, m), 2.73 (3H, s), 3.52-3.62 (2H, m), 4.07-4.17 (2H, m), 4.33 (2H, q, *J* = 7.0 Hz), 4.72 (2H, s), 7.26-7.27 (2H m), 7.37-7.39 (3H, m), 7.47 (1H, s), 8.35 (1H, s). MS $^m/_z$: 485 (M+1).

Ejemplo 31

N-(Bencilsulfonil)-1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxamida

(a) *terc*-Butil 4-{[(bencilsulfonil)amino]carbonil}piperidin-1-carboxilato

Trietilamina (591 g, 5840 mmol) se agregó a una suspensión agitada de ácido 1-(*terc*-butoxicarbonil)piperidin-4-carboxílico (448 g, 1954 mmol), LiCl (23.1 g, 545 mmol) y TBTU (657 g, 2046 mmol) en THF (3000 mL) bajo una atmósfera de nitrógeno a temperatura de la sala. Una solución de 1-fenilmetanosulfonamida (352 g in 1300 mL THF, 2056 mmol) se agregó después de 1.5 horas y la agitación se continuó de un día para otro. El disolvente se retiró *in vacuo* para producir una mezcla café claro-gris espesa (volumen alrededor de 2500 mL). Se agregó EtOAc (3500 mL), seguido por una solución acuosa de HCl (1960 mL 3.6 M HCl y 1960 mL de agua). Se retiró la fase acuosa y la fase orgánica se lavó con 2 x 1500 mL 1 M HCl. La fase orgánica se enfrió a 0°C, lo cual produjo un precipitado de HOBt, el cual se extrajo completamente por filtración. La mayor parte del disolvente se retiró *in vacuo* para producir una mezcla café claro-gris espesa. Se agregó EtOH (50%, 4000 mL) y la mezcla se agitó durante 1.5 horas. El producto precipitado se extrajo completamente por filtración, se lavó con 50% EtOH (500 mL + 2 x 1500 mL) y se secó en un horno de

vacío a 25 °C para producir *terc*-butil 4-[(bencilsulfonil)carbamoil] piperidin-1-carboxilato como un sólido blanco. Rendimiento: 584 g (78%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s), 1.54-1.61 (2H, m), 1.70-1.74 (2H, m), 2.19-2.27 (1H, m), 2.68-2.75 (2H, m), 4.07-4.12 (2H, m), 4.66 (2H, s), 7.32-7.41 (5H, m), 7.54 (1H, br s).

(b) N-(bencilsulfonil)piperidin-4-carboxamida

terc-Butil 4-[(bencilsulfonil)carbamoil]piperidin-1-carboxilato (583 g, 1524 mmol) se suspendió en ácido fórmico (3000 mL) bajo una atmósfera de nitrógeno y la reacción se agitó durante 20 minutos. La reacción presentó espumación debido a la evolución de gas, y se empleó ácido fórmico (500 mL) para retirar por lavado la espuma de las paredes del recipiente de reacción. Luego de 2 horas la espumación se había detenido y la reacción se aclaró con unos pocos sólidos remanentes. La reacción se agitó de un día para otro y se retiraron 2500 ml de ácido fórmico *in vacuo*. Se agregó agua (1000 mL) y la reacción se filtró. La solución clara se evaporó y se agregó agua (3000 mL). Se empleó una solución de hidróxido de amonio saturado en agua (se agregó un total de 390 mL y el pH subió de 3.10 a 6.10) para neutralizar la solución ácida y en el criterio de valoración (pH=6.10) se formó un precipitado pesado del producto. La mezcla se agitó de un día para otro y el precipitado se extrajo completamente por filtración y se lavó con agua (1000 mL). El secamiento en un horno de vacío a 25°C produjo N-(bencilsulfonil)piperidin-4-carboxamida como un polvo blanco. Rendimiento: 372.4 g (87%).
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.60-1.72 (2H, m), 1.75-1.84 (2H, m), 2.10-2.19 (1H, m), 2.77-2.87 (2H, m), 3.10-3.18 (2H, m), 4.23 (2H, s), 7.18-7.28 (5H, m), 8.17 (1H, br s).

(c) *N*-(Bencilsulfonil)-1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxamida

Una suspensión de 2,3-dicloro-5-(5-etil-1,3-oxazol-2-il)piridina (0.300 g, 1.23 mmol), N-(bencilsulfonil)piperidin-4-carboxamida (0.367 g, 1.30

mmol) y DIPEA (0.645 mL, 3.70 mmol) in DMA (10 mL) se agitó a 80°C durante 24 horas. La mezcla de reacción se enfrió a temperatura de la sala y se virtió en EtOAc (60 mL) y NH_4Cl saturado (30 mL). Los orgánicos se lavaron 30 con agua (3 x 50 mL), salmuera (1 x 50 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (3:7 EtOAc / hexanos con 0.5% AcOH) proporcionó *N*-(bencilsulfonil)-1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]piperidin-4-carboxamida como un sólido. Rendimiento: 0.297 g (49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (3H, t, *J* = 7.0 Hz), 1.86-1.91 (4H, m), 2.29-2.38 (1H, m), 2.75 (2H, q, *J* = 7.0 Hz), 2.84-2.91 (2H, m), 3.97-4.02 (2H, m), 4.69 (2H, s), 6.82 (1H, s), 7.35-7.41 (5H, m), 7.47 (1H, br s), 8.15 (1H, d, *J* = 2.0 Hz), 8.74 (1H, d, *J* = 2.0 Hz). MS $^m/_z$: 489 (M+1).

Ejemplo 32

Ciclopentil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-metilnicotínico

(a) Ciclopentanolato de sodio

Alcohol ciclopentílico (5 mL) se enfrió a 0 °C. Se agregó lentamente hidruro de sodio (95%, 0.018 g, 0.713 mmol). La solución se utilizó cruda asumiendo una conversión del 100%.

(b) Ciclopentil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-metilnicotínico

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il-nicotínico (0.070 g, 0.158 mmol, véase Ejemplo 46) y mallas moleculares (4 Ångstrom, 0.070 g) se suspendieron en ciclopentanol (5 mL) y DMSO (2 mL) y se agitaron a temperatura de la sala durante 10 minutos. Se agregó ciclopentanolato de sodio (0.286 g, 3.48 mmol) en alcohol ciclopentílico (5 mL) y la solución se agitó durante 10 minutos. HCl (concentrado) se agregó gota a gota a la mezcla hasta que el pH se redujo a pH 2. La mezcla de reacción se filtró y luego se concentró bajo presión

reducida. Se agregó agua (10 mL) a la solución y los acuosos combinados se lavaron con EtOAc (3 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (30% EtOAc con 0.5% AcOH) produjo ciclopentil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.031 g (41%).
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.56-1.64 (2H, m), 1.69-1.80 (4H, m), 1.84-1.95 (2H, m), 2.63 (3H, m) 3.52-3.60 (1H, m), 4.26-4.35 (2H, m), 4.37-4.45 (2H, m), 4.76 (2H, s) 5.22-5.30 (1H, m), 7.31-7.43 (5H, m) 8.29 (1H, s), 11.8 (1H, s). MS $^m/_z$: 483 (M+1).

Ejemplo 33

Propil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico

A una solución de etil éster de ácido 6-(4-{[(bencilsulfonil)amino] carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico (0.078 g, 0.17 mmol, Véase Ejemplo 42) en THF (15 mL) y n-propanol (15 mL) se agregaron mallas moleculares de 4 Ångstrom (0.5 g). La mezcla de reacción se agitó durante 1 hora y luego se enfrió a 0°C. Después de la adición de NaH (60% dispersión en aceite mineral, 0.013 g, 0.33 mmol), la mezcla se calentó a temperatura de la sala y se agitó durante 2 horas. La adición de ácido acético (5.0 mL), la filtración a través de celita, la concentración seguida por destilación bajo una temperatura fija (***"azeotroping"***) con tolueno (2 x 50 mL) proporcionaron el material crudo. La trituración con MeOH (1 x 25 mL) y luego EtOAc (1 x 25 mL) proporcionó propil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil} piperidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.027 g (34%).
^{1}H NMR (400 MHz, DMSO- d_6): δ 0.96 (3H, t, J = 7.5 Hz), 1.59-1.66 (2H, m), 1.67-1.76 (2H, m), 1.82-1.86 (2H, m), 2.55-2.62 (1H, m), 2.65 (3H, s), 3.11-3.17 (2H, m), 4.17 (2H, t, J = 6.7 Hz), 4.56-4.52 (2H, m), 4.70 (2H, s), 7.28-7.31 (2H, m), 7.38-7.43 (3H, m), 8.34 (1H, s), 11.61 (1H, br s). MS $^m/_z$: 485 (M+1).

Ejemplo 34

Etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-isopropilnicotínico

(a) Etil 2-((dimetilamino)metilen)-4-metil-3-oxopentanoato

1,1-Dimetoxi-N,N-dimetilmetanamina (4.96 mL, 37.2 mmol) se agregó gota a gota a etil 4-metil-3-oxopentanoato (5.00 mL, 31.0 mmol), agitando simultáneamente a temperatura de la sala. La mezcla de reacción se dejó agitar a temperatura de la sala durante 18 horas y luego se concentró bajo presión reducida y se destiló a temperatura fija con tolueno (2 x 20 mL) produciendo etil 2-((dimetilamino)metilen)-4- metil-3-oxopentanoato como un aceite, el cual se utilizó sin purificación. Rendimiento: 6.61 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (6H, d, J = 6.9 Hz), 1.31 (3H, t, J = 7.3 Hz), 3.00 (6H, br s), 3.26 (1H, br s), 4.21 (2H, q, J = 7.3 Hz), 7.60 (1H, s).

(b) Etil 5-ciano-2-isopropil-6-oxo-1,6-dihidropiridin-3-carboxilato

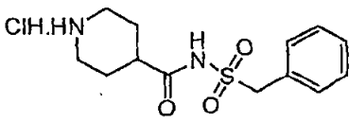
A una suspensión de 2-cianoacetamida (2.74 g, 32.6 mmol) en THF (100 mL) se agregó NaH (60% dispersión en aceite mineral, 1.36 g, 34.1 mmol). El sistema se agitó a temperatura de la sala hasta que cesó la evolución, punto en el cual se agregó etil 2-((dimetilamino)metilen)-4-metil-3-oxopentanoato (6.61 g, 31.0 mmol) en una porción. La mezcla de reacción se agitó a temperatura de la sala durante 18 horas y se concentró bajo presión reducida para proporcionar el intermedio crudo. Los sólidos se disolvieron en una cantidad mínima de agua caliente y luego se acidificaron a pH 1 con 5 N HCl. La filtración seguida por secamiento bajo vacío produjo etil 5-ciano-2-isopropil-6-oxo-1,6-dihidropiridin-3-carboxilato. Rendimiento: 6.46 g (89%).

^{1}H NMR (400 MHz, DMSO- d_6): δ 1.25 (6H, d, J = 7.1 Hz), 1.29 (3H, t, J = 7.3 Hz), 4.01- 4.12 (1H, m), 4.23 (2H, q, J = 7.3 Hz), 8.43 (1H, s), 12.56 (1H, br s). MS $^m/_z$: 235 (M+1).

(c) Etil 6-cloro-5-ciano-5-isopropilnicotinato

Una suspensión de etil 5-ciano-2-isopropil-6-oxo-1,6-dihidropiridin-3-carboxilato (6.46 g, 27.6 mmol) en $POCl_3$ (10.1 mL, 110 mmol) se calentó a 100°C durante 6 horas. La mezcla de reacción se virtió en hielo y luego se basificó con K_2CO_3 sólido. La fase acuosa se extrajo con DCM (3 x 100 mL) y los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar etil 6-cloro-5-ciano-2-isopropilnicotinato, el cual se utilizó sin purificación adicional. Rendimiento: 6.54 g (93%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (6H, d, J = 6.8 Hz), 1.42 (3H, t, J = 7.2 Hz), 3.88-3.98 (1H, m), 4.41 (2H, q, J = 7.2 Hz), 8.37 (1H, s). MS $^m/_z$: 254 (M+1).

(d) Clorhidrato de *N*-(Benzilsulfonil)piperidin-4-carboxamida



A una suspensión de *terc*-butil 4-{[(bencilsulfonil)amino]carbonil} piperidin-1-carboxilato (4.18 g, 10.9 mmol) en THF (100 mL) se agregó 4 M HCl en dioxano (54.6 mL, 218 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 18 horas. Los sólidos se recogieron por filtración y se lavaron con EtOAc (100 mL) y luego se pusieron bajo vacío para proporcionar clorhidrato de N-(bencilsulfonil)piperidin-4-carboxamida como un sólido. Rendimiento: 2.50 g (72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.70-1.78 (2H, m), 1.83-1.88 (2H, m), 2.47-2.53 (1H, m), 2.80-2.89 (2H, m), 3.26-3.31 (2H, m), 4.71 (2H, s), 7.27-7.30 (2H, m), 7.39-7.41 (3H, m), 8.53 (1H, br s), 8.79 (1H, br s), 11.70 (1H, br s).

(e) Etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-isopropilnicotínico

Una mezcla de etil 6-cloro-5-ciano-2-isopropilnicotinato (0.184 g, 0.728 mmol), clorhidrato de N-(bencilsulfonil)piperidin-4-carboxamida (0.232 g,

0.728 mmol) y DIPEA (0.380 mL, 2.18 mmol) en DMF (3.0 mL) se calentó a 60°C durante 5 horas. La mezcla de reacción se diluyó con EtOAc (30 mL), se lavó con NH_4Cl saturado (2 x 15 mL) y salmuera (15 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (DCM seguido por 1% MeOH, 1% HOAc en DCM) produjo un sólido, el cual se trituró con 1:1 Et_2O/hexanos (25 mL) para proporcionar etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-isopropilnicotínico como un sólido. Rendimiento: 0.300 g (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (6H, d, J = 6.5 Hz), 1.38 (3H, 1, J = 7.3 Hz), 1.74-1.90 (4H, m), 2.41-2.48 (1H, m), 3.11-3.18 (2H, m), 3.95-4.05 (1H, m), 4.32 (2H, q, J = 7.3 Hz), 4.64-4.69 (4H, m), 7.31-7.33 (2H, m), 7.37-7.43 (3H, m), 8.10 (1H, br s), 8.31 (1H, s). MS $^m/_z$: 499 (M+1).

Ejemplo 35

Etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-etilnicotínico

(a) Etil 2-((dimetilamino)metilen)-3-oxopentanoato

1,1-Dimetoxi-N,N-dimetilmetanamina (5.09 mL, 42.0 mmol) se agregó gota a gota a etil 3-oxopentanoato (5.0 mL, 35.0 mmol), agitando simultáneamente a temperatura de la sala. La mezcla de reacción se agitó a temperatura de la sala durante 18 horas y luego se concentró bajo presión reducida y se destiló a temperatura fija con tolueno (2 x 20 mL) produciendo etil 2-((dimetilamino)metilen)-3-oxopentanoato como un aceite el cual se utilizó sin purificación. Rendimiento: 6.98 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (3H, t, J = 7.7 Hz), 1.32 (3H, t, J = 7.7 Hz), 2.67-2.69 (2H, m), 3.01 (6H, br s), 4.22 (2H, q, J = 7.2 Hz), 7.64 (1H, s).

(b) Etil 5-ciano-2-etil-6-oxo-1,6-dihidropiridin-3-carboxilato

A una suspensión de 2-cianoacetamida (3.09 g, 36.8 mmol) en THF (100 mL) se agregó NaH (60% dispersión en aceite mineral, 1.54 g, 38.5 mmol). La mezcla se agitó a temperatura ambiente hasta que cesó la evolución de gas, punto en el cual se agregó en una porción etil 2-((dimetilamino)metilen)-3-oxopentanoato (6.98 g, 35.0 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 18 horas y se concentró bajo presión reducida para proporcionar el intermedio crudo. Los sólidos se disolvieron en una cantidad mínima de agua caliente y luego se acidificó a pH 1 con 5 M HCl. La filtración seguida por secamiento bajo vacío produjo etil 5-ciano-2-etil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido. Rendimiento: 6.28 g (81%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (3H, t, J = 7.3 Hz), 1.29 (3H, t, J = 7.0 Hz), 2.95 (2H, q, J = 7.3 Hz), 4.24 (2H, q, J = 7.0 Hz), 8.45 (1H, s), 12.79 (1H, br s). MS $^m/_z$: 221 (M+1).

(c) Etil 6-cloro-5-ciano-2-etilnicotinato

Una suspensión de etil 5-ciano-2-etil-6-oxo-1,6-dihidropiridin-3-carboxilato (6.28 g, 28.5 mmol) en POCk (10.4 mL, 114 mmol) se calentó a 100°C durante 6 horas. La mezcla de reacción se virtió en hielo y luego se basificó con K_2CO_3 sólido. La fase acuosa se extrajo con DCM (3x 100 mL) y los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar etil 6-cloro-5-ciano-2-etilnicotinato como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 6.17 g (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (3H, t, J = 7.4 Hz), 1.42 (3H, t, J = 7.4 Hz), 3.23 (2H, q, J = 7.4 Hz), 4.42 (2H, q, J = 7.4 Hz), 8.45 (1H, s). MS $^m/_z$: 239 (M+1).

(d) Etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-etilnicotínico

Una solución de etil 6-cloro-5-ciano-2-etilnicotinato (0.143 g, 0.599 mmol), clorhidrato de N-(bencilsulfonil)piperidin-4-carboxamida (0.191 g, 0.599

mmol, Véase Ejemplo 34(d)) y DIPEA (0.131 mL, 1.80 mmol) en DMF (3.0 mL) se calentó a 60°C durante 5 horas. La mezcla de reacción se diluyó con EtOAc (30 mL), se lavó con NH_4Cl saturado (2 x 15 mL) y salmuera (15 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (DCM seguido por 1% MeOH, 1% HOAc en DCM) produjo un sólido, el cual se trituró con 1:1 Et_2O/hexanos (25 mL) para proporcionar etil éster de ácido 6-(4-{[(bencilsulfonil)amino] carbonil}piperidin-1-il)-5-ciano-2-etilnicotínico como un sólido. Rendimiento: 0.250 g (84%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.4 Hz), 1.38 (3H, t, J = 7.0 Hz), 1.74-1.82 (2H, m), 1.84-1.90 (2H, m), 2.39-2.47 (1H, m), 3.10-3.18 (4H, m), 4.32 (2H, q, J = 7.0 Hz), 4.66-4.70 (4H, m), 7.32-7.35 (2H, m), 7.38-7.42 (3H, m), 7.70 (1H, br s), 8.35 (1H, s). MS $^m/_z$: 485 (M+1).

Ejemplo 36

2,2-Dimetilpropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-metilnicotínico

(a) Ácido 1-{3-ciano-5-[(2,2-dimetilpropoxi)carbonil]-6-metilpiridin-2-il} azetidin-3-carboxílico

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.218 g, 0.92 mmol) se suspendió en THF (20 mL) y DMSO (4 mL) y se agregó 2,2-dimetilpropan-1-olato de sodio (3.684 mL, 3.684 mmol). La mezcla de reacción se agitó a temperatura de la sala hasta que se observó la completa conversión del material de partida por análisis HPLC. La reacción se detuvo con 1 N HCl (10 mL) y la mezcla de reacción se diluyó con agua (50 mL) y se extrajo en EtOAc (2 x 40 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (3:7 EtOAc/hexanos, 0.5% AcOH a 1:1 EtOAc/hexanos, 0.5% AcOH) produjo ácido 1-{3-ciano-5-[(2,2-dimetilpropoxi)carbonil]-6-metilpiridin-2-il} azetidin-3-carboxílico como un sólido. Rendimiento: 0.167 g (55%).

(b) 2,2-Dimetilpropil éster de ácido 6-(3-{[(bencilsulfonil)amino) carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico

Ácido 1-{3-ciano-5-[(2,2-dimetilpropoxi)carbonil]-6-metilpiridin-2-il} azetidin-3-carboxílico (0.080 g, 0.24 mmol), EDCI (0.060 g, 0.31 mmol) y HOBt (0.042 g, 0.31 mmol) se disolvieron en DCM (5 mL) a temperatura de la sala La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos y luego se agregaron fenilmetanosulfonamida (0.058 g, 0.34 mmol) y DIPEA (0.25 mL, 1.45 mmol). La mezcla de reacción se agitó a temperatura de la sala hasta que se observó un consumo completo del material inicial por análisis HPLC. La mezcla de reacción se diluyó con DCM (20 mL) y se lavó con NH_4Cl (20 mL) saturado. Los orgánicos combinados se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (3:7 EtOAc/hexanos, 0.5% AcOH a 1:1 EtOAc/hexanos, 0.5% AcOH), seguida por HPLC preparativa produjo 2,2-dimetilpropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.016 g (14%). ^{1}H NMR (400 MHz, CDl_3): δ 1.02 (9H, s), 2.74 (3H, s), 3.26-3.56 (1H, m), 3.97 (2H, s), 4.43-4.50 (4H, m), 4.69 (2H, s), 7.36-7.56 (5H, m), 8.27 (1H, s). MS $^m/_z$: 485 (M+1).

Ejemplo 37

***N*-(Bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida**

(a) Etil 5-ciano-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxilato

La sal de sodio de etil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (8.81 g, 38.6 mmol) se distribuyó por partes iguales en 8 frascos de proceso Smith. A cada frasco se agregó DCM (3 mL), [2-(clorometoxi) etil](trimetil)silano (1.78 g,10.7 mmol), y luego DIPEA (2.07 g, 16.0 mmol). Cada frasco se calentó en un horno microondas, calentamiento de

nodo simple, a 120° C durante 10 minutos. Se agregó más [2-(clorometoxi)etil](trimetil)silano (0.445 g, 2.68 mmol) a cada frasco y se continuó el calentamiento de nodo simple a 120°C durante 10 minutos. Las mezclas de reacción se combinaron y se filtraron en vacío. La purificación por cromatografía instantánea en SiO_2 con heptano/EtOAc 4:1 o 3:1 proporcionó el producto puro. Rendimiento: 8.376 g (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 5.46 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.52 (t, J = 8.0 Hz, 2H), 2.78 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.75 (t, J = 8.0 Hz, 2H), -0.18 (s, 9 H). MS $^m/_z$: 335 (M-1).

(b) Ácido 5-ciano-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-6-carboxílico

Etil 5-ciano-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxilato (8.371 g, 24.9 mmol) se disolvió en THF (50 mL) y se agregó 1M LiOH (100 mL). La mezcla de reacción se agitó a temperatura de la sala durante 3 horas. La conversión se completó de acuerdo con LC/MS. Se agregó 4M HCl a pH 2-3. La fase acuosa se extrajo con EtOAc (3x100 mL). Las fases orgánicas se combinaron y secaron con sulfato de sodio y se evaporaron para producir un material crudo. Rendimiento: 8.35 g (109%). El etil 5-ciano-2-metil-6-{[2-(trimetilsilil)etoxi]metoxi}nicotinato isomérico se formó como el principal producto de acuerdo con LC/MS, la cual mostró una relación de producto/sub-producto de 25:75. No se intentó separar los isómeros.
MS $^m/_z$: 307 (M-1).

(c) 5-Ciano-*N*-(2-hidroxibutil)-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxamida

Una mezcla (7.67 g, 24.9 mmol) de ácido 5-ciano-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxílico y el isómero etil 5-ciano-2-metil-6-{[2-(trimetilsilil)etoxi]metoxi}nicotinato, en una relación de 25:75, de acuerdo con LC/MS, se disolvió en DCM (125 mL). Se agregaron EDCI (6.2 g, 27.4 mmol) y HOBt (5.04 g, 37.3 mmol) y la

mezcla de reacción se agitó a temperatura de la sala durante 40 minutos. Se agregó 1-aminopropan-2-ol (2.44 g, 27.7 mmol) en DIPEA (16.1 g, 124.4 mmol) y se continuó la agitación a temperatura de la sala durante 1.5 horas. De acuerdo con LC/MS sólo el isómero menor se había convertido en este punto. Se continuó la agitación a temperatura de la sala durante 16 horas más sin ningún cambio en LC/MS. La fase orgánica se extrajo con 10% carbonato de potasio (2x125 mL), salmuera (2x125 mL), se secó con sulfato de sodio y se evaporó. Esto proporcionó 12.21 g de producto crudo. La purificación por cromatografía instantánea en gel de sílice con fracciones de heptano/EtOAc, primero 1:2, luego1:4, eluidas proporcionó 5-ciano-*N*-(2-hidroxibutil)-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxamida. Rendimiento: 3.28 g (35%). Cuando todo el producto se hubo eluido, la elución se realizó con heptano/EtOAc 1:4 + 1% ácido fórmico. De este modo, se recuperaron 2.46 g de etil 5-ciano-2-metil-6-{[2-(trimetilsilil) etoxi]metoxi}nicotinato.

^{1}H NMR (400 MHz, $CDCl_3$): δ -0.13 (s, 9H), 0.87-0.77 (m, 5H), 1.44-1.31 (m, 2H), 2.58 (s, 3H), 3.15-3.06 (m, 1H), 3.46-3.38 (m, 1H), 3.60-3.50 (m, 4H), 5.41 (s, 2H), 7.26-7.21 (m, 1H), 7.77 (s, 1H). MS $^m/_z$: 378 (M-1).

(d) 5-Ciano-2-metil-6-oxo-*N*-(2-oxobutil)-1-{[2-(trimetilsilil)etoxi] metil}-1,6-dihidropiridin-3-carboxamida

Cloruro de oxalilo (0.39 g, 3.05 mmol) se disolvió en DCM (2 mL) bajo una atmósfera de nitrógeno y la solución se enfrió a -78 °C. Se agregó DMSO (0.37 g, 4.69 mmol) en DCM (1 mL) gota a gota y la mezcla se agitó a -78 °C durante menos de 5 minutos. Se agregó 5-ciano- *N*-(2-hidroxibutil)-2-metil-6-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxamida (0.89 g, 2.35 mmol) en DCM (2 mL) durante 2 minutos y se continuó la agitación a -78 °C durante 1 hora. Se agregó TEA (1.19 g, 11.7 mmol). Después de agitar durante 15 minutos, se retiró el baño de enfriamiento y la mezcla de reacción se agitó a temperatura ambiente durante 15 minutos. Se agregó agua (10 mL) y la fase acuosa se extrajo con DCM (3x15 mL). Las fases orgánicas se combinaron y secaron

con sulfato de sodio y se evaporaron para producir el producto crudo, el cual se utilizó sin purificación adicional. Rendimiento: 0.780 g (88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ -0.12 (s, 9H), 0.81 (t, J = 8.2 Hz, 2H), 0.97 (t, J = 7.4 Hz, 2H), 2.40 (q, J = 7.4 Hz, 2H), 2.63 (s, 3H), 3.55 (t, J = 8.2 Hz, 2H), 4.09 (d, J = 5.3 Hz, 2H), 5.45 (s, 2H), 7.50 (t, J = 5.3 Hz, 1H), 7.86 (s, 1H). MS $^m/_z$: 376 (M-1).

(e) **5-(5-Etil-1,3-oxazol-2-il)-6-metil-2-oxo-1-{[2-(trimetilsilil) etoxi] metil}-1,2-dihidropiridin-3-carbonitrilo**

5-Ciano-2-metil-6-oxo-N-(2-oxobutil)-1-{[2-(trimetilsilil)etoxi]metil}-1,6-dihidropiridin-3-carboxamida (2.761 g, 7.31 mmol) se disolvió en THF (9.6 mL) y la solución se transfirió por partes iguales en e frascos de proceso Smith. A cada frasco se agregó hidróxido de (metoxicarbonilsulfamol) trietilamonio, sal interna (1.162 g, 4.88 mmol). Los frascos se sellaron y se calentaron en un horno microondas, calentamiento de nodo simple, a 80 °C durante 2 minutos. LC/MS sobre cada vial mostró la completa conversión. Las mezclas de reacción se combinaron y se evaporaron para producir 6.431 g de un material crudo. La filtración a través de un tapón de silicio (10 g) con heptano/EtOAc 1:1 (100 mL) proporcionó 5-(5-etil-1,3-oxazol-2-il)-6-metil-2-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,2-dihidropiridin-3-carbonitrilo. Rendimiento: 1.766 g (67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ -0.20 (s, 9H), 0.74 (t, J = 8.0 Hz, 2H), 1.09 (t, J = 7.5 Hz, 3H), 2.55 (q, J = 7.5 Hz, 2H), 2.82 (s, 3H), 3.52 (t, J = 8.0 Hz, 2H), 5.46 (s, 2H), 6.62 (s, 1H), 8.09 (s, 1H). MS $^m/_z$: 358 (M-1).

(f) 5-(5-Etil-1,3-oxazol-2-il)-6-metil-2-oxo-1,2-dihidropiridin-3-carbonitrilo

Una mezcla TFA/DCM (1:1, 10 mL) se agregó a (5-(5-etil-1,3-oxazol-2-il)-6-metil-2-oxo-1-{[2-(trimetilsilil)etoxi]metil}-1,2-dihidropiridin-3-carbonitrilo (1.682 g, 4.68 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 4 horas. De acuerdo con LC/MS, la reacción se completó. La mezcla de reacción se evaporó. Se agregó DCM (10 mL)

y la mezcla se secó con sulfato de sodio y se evaporó. Esto produjo 0.263 g de material crudo. La purificación por cromatografía instantánea en gel de silicicio con DCM/MeOH (69:1, luego 39:1) proporcionó el compuesto del título. Rendimiento: 0.263 g (82%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (br t, J = 7.5 Hz, 3H), 2.68 (s, 3H), 2.73 (br q, J = 7.5 Hz, 2H), 7.00 (br s, 1H), 8.51 (s, 1H), 12.97 (s, 1H). MS $^m/_z$: 230 (M+1).

(g) 2-Cloro-5-(5-etil-1,3-oxazol-2-il)-6-metilnicotinonitrilo

5-(5-Etil-1,3-oxazol-2-il)-6-metil-2-oxo-1,2-dihidropiridin-3-carbonitrilo (0.069 g, 0.30 mmol) se disolvió en DCM (0.8 mL) en un frasco de proceso Smith, y se agregaron a 0 °C cloruro de oxalilo (0.573 g, 4.51 mmol) y luego DMF (0.022 g, 0.3 mmol). La mezcla de reacción se calentó en el frasco sellado en un baño de aceite a 50 °C durante 2.5 horas. LC/MS mostró 33% del producto deseado y 45% del material de partida. Se continuó la agitación a la misma temperatura. Después de 1.5 horas más, se agregó más DMF (0.022 g, 0.30 mmol). Se realizó agitación a la misma temperatura durante 7.5 horas más. LC/MS mostró 64% del producto deseado y 8% del material de partida. La mezcla de reacción se evaporó y se mezcló con un lote que se preparó en la siguiente forma:

5-(5-Etil-1,3-oxazol-2-il)-6-metil-2-oxo-1,2-dihidropiridin-3-carbonitrilo (0.179 g, 0.78 mmol) se disolvió en DCM (2.4 mL) en un frasco de proceso Smith, y se agregaron cloruro de oxalilo (1.486 g, 11.70 mmol) y luego DMF (0.057 g, 0.78 mmol) a 0 °C. La mezcla de reacción se calentó en el frasco sellado en un baño de aceite a 50 °C durante 4 horas. LC/MS mostró 40% del producto deseado y 22% de material de partida. Se agregó más DMF (0.057 g, 0.78 mmol). Se realizó agitación a la misma temperatura durante 16 horas más. LC/MS mostró 35% del producto deseado y nada de material de partida. El material se evaporó. La purificación de los lotes combinados se hizo por cromatografía instantánea en gel de silicio con DCM/MeOH 199:1 como eluyente para proporcionar 2- cloro-5-(5-etil-1,3-oxazol-2-il)-6-metilnicotinonitrilo. Rendimiento: 0.027g (10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, J = 7.5 Hz, 3H), 2.80 (q, J = 7.5 Hz, 2H), 3.00 (s, 3H), 6.97 (s, 1H), 8.52 (s, 1H).

(h) Acido 1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il] piperidin-4-carboxílico

2-Cloro-5-(5-etil-1,3-oxazol-2-il)-6-metilnicotinonitrilo (0.056 g, 0.23 mmol) se disolvió en EtOH seco (4 mL) en un frasco de proceso Smith. Se agregó ácido piperidin-3-carboxílico (0.051 g, 0.40 mmol) y el frasco sellado se calentó en un horno microondas, calentamiento de nodo simple, a 120 °C durante 20 minutos. LC/MS mostró que la reacción no estaba completa. Se agregaron TEA (0.233 g, 2.30 mmol) y más ácido piperidin-3-carboxílico (0.015 g, 0.11 mmol) y el frasco sellado se calentó luego en un horno microondas, calentamiento de nodo simple, a 100 °C durante 20 minutos. LC/MS mostró que la reacción estaba completa. La mezcla de reacción se evaporó. Se agregó 1M HCl (3 mL) y la mezcla se extrajo con DCM (3x3 mL) empleando un separador de fase. Esto proporcionó el producto crudo el cual se utilizó sin purificación adicional. Rendimiento: 0.086 g (110%)

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J = 7.5 Hz, 3H), 1.78-1.62 (m, 2H), 1.99-1.86 (m, 2H), 2.51-2.39 (m, 1H), 2.67-2.57 (m, 5H), 3.16-3.04 (m, 2H), 4.43-4.32 (m 2H), 6.70 (br s, 1H), 8.11 (s, 1H). MS $^m/_z$: 341 (M+1).

(i) *N*-(Bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida

Ácido 1-[3-ciano-5-(5-etil-1,3-oxazo-2-il)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.026 g, 0.0075 mmol) se disolvió en DMF (1 mL); se agregaron HATU (0.034 g, 0.090 mmol) y DIPEA (0.048 g, 0.38 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 15 minutos antes de agregar 1-fenilmetanosulfonamida (0.013 g, 0.075 mmol). Se continuó la agitación a temperatura de la sala durante 4 horas. De acuerdo con LC/MS, cerca de la mitad del material de partida se había convertido en este punto. Se agregó más 1-fenilmetanosulfonamida (0.013 g, 0.075

mmol) y se continuó la agitación a temperatura de la sala durante el fin de semana (64 horas). LC/MS mostró sólo alrededor de la mitad del material de partida se había convertido. Se agregó más HATU (0.028 g, 0.075 mmol) y se continuó la agitación a temperatura de la sala durante 5.5 horas más. De acuerdo con LC/MS, la reacción se había completado en este punto. La purificación por HPLC preparativa proporcionó el producto puro. Rendimiento: 0.024 g (64%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, J =7.6 Hz, 3H), 1.74-1.61 (m, 2H), 1.90-1.81 (m, 2H), 2.58-2.54 (m, 1H), 2.79-2.72 (m, 5H), 3.17-3.08 (m, 2H), 4.51-4.44 (m, 2H), 4.70 (s, 2H), 7.04 (s, 1H), 7.34-7.29 (m, 2H), 7.45-7.39 (m, 3H), 8.38 (s, 1H), 11.62 (s, 1H). MS $^m/_z$: 494 (M+1).

Ejemplo 38

Isopropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico

(a) Propan-2-olato de sodio

Alcohol isopropílico (5 mL) se enfrió a 0 °C. Lentamente se agregó hidruro de sodio (95%, 0.088 g, 3.48 mmol). La solución se usó cruda asumiendo una conversión del 100%.

(b) Ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.400 g, 1.20 mmol) se disolvió alcohol isopropílico (5 mL) y se agitó a temperatura de la sala durante 10 minutos. Se agregó propan-2-olato de sodio (0.286 g, 3.48 mmol) en alcohol isopropílico (5 mL) y la solución se agitó durante 10 minutos. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. La mezcla de reacción se concentró bajo presión reducida. La mezcla de reacción se concentró bajo presión reducida. El acuoso se lavó con EtOAc (3 x 40 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el

producto crudo como un sólido. Cromatografía instantánea (100% EtOAc a 100% EtOAc con 0.5% AcOH) produjo ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico como un sólido. Rendimiento: 0.133 g (51.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (6H, d, J = 6.2 Hz), 2.71 (3H, s), 3.59-3.67 (1H, m), 4.57-4.64 (4H, m), 5.15-5.24 (1H, m), 8.26 (1H, s). MS $^m/_z$: 304 (M+1).

(c) Isopropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-metilnicotínico

Ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.047 g, 0.153 mmol), EDCI (0.035 g, 0.184 mmol) y HOBt (0.025 g, 0.184 mmol) se disolvieron en DCM (1 mL) a temperatura de la sala. La mezcla de reacción se agitó a temperatura de la sala durante 30 minutos y luego se agregaron 1-fenilmetanosulfonamida (0.032 g, 0.184 mmol) y DIPEA (0.134 mL, 0.767 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. La trituración (4:1 hexanos/CH_2Cl_2) produjo isopropil éster de ácido 6-(3-{[(bencilsulfonil) amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 0.031 g (44.3%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 2.64 (3H, s), 3.52-3.59 (1H, m), 4.29-4.44 (4H, m), 4.75 (2H, m), 5.04-5.10 (1H, m), 7.32-7.40 (5H, m), 8.29 (1H, s), 11.8 (1H, s). MS $^m/_z$: 457 (M+1).

Ejemplo 39

Isopropil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil} piperidin-1-il)-5-ciano-2-metilnicotínico

(a) Isopropil 2-((dimetilamino)metilen)-3-oxobutanoato

Isopropil 3-oxobutanoato (200 mL, 1365 mmol) se agitó a temperatura de la sala y dimetoxi-N,N-dimetilmetanamina (242 mL, 1706 mmol) se agregó gota a gota. La mezcla de reacción se dejó agitar a temperatura de la sala de un día para otro. La mezcla de reacción se concentró bajo vacío y luego se destiló a temperatura fija con tolueno (3 ' 300 mL) y se puso bajo alto vacío para proporcionar isopropil 2-((dimetilamino)metilen)-3-oxobutanoato como un aceite, el cual se utilizó sin purificación adicional. Rendimiento: 272 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (6H, d, J = 6.2 Hz), 2.32 (3H, s), 5.07-5.17 (1H, m); 7.64 (1H, s).

(b) Isopropil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

NaH (33.359 g, 834.07 mmol) se suspendió en THF (700 mL) y se agregó 2-cianoacetamida (58.905 g, 700.62 mmol) en porciones a temperatura de la sala. Una vez detenida la evolución de gas, se agregó una solución de isopropil 2-((dimetilamino)metilen)-3-oxobutanoato (147.72 g, 667.25 mmol) en THF (300 mL) y el sistema se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se concentró bajo presión reducida y los sólidos se disolvieron en la cantidad mínima de agua caliente. 1N HCl se agregó a la solución hasta un pH 1 y los sólidos se aislaron mediante filtración. Los sólidos se secaron bajo alto vacío para proporcionar isopropil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido, el cual se utilizó sin purificación adicional. Rendimiento:
30 123 g (84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (6H, d, J = 6.2 Hz), 2.84 (3H, s), 5.18-5.28 (1H, m), 8.50 (1H, s), 13.04 (1H, s). MS $^m/_z$: 221 (M+1).

(c) Isopropil 6-cloro-5-ciano-2-metilnicotinato

Isopropil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (123.04 g, 558.70 mmol) se suspendió en $POCl_3$ (204.58 mL, 2234.8 mmol) y se calentó a 100 °C durante 5 horas. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. El residuo se diluyó con DCM y se virtió sobre hielo. La mezcla bi-fásica se agitó a temperatura de la sala y se extinguió lentamente con K_2CO_3 sólido hasta que todo el $POCl_3$ se había hidrolizado. Se extrajo el acuoso en DCM y los orgánicos, se secaron ($MgSO_4$) y se pasaron a través de un tapón de sílice. Los orgánicos se concentraron bajo presión reducida para proporcionar isopropil 6-cloro-5-ciano-2-metilnicotinato como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 106 g (79%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (6H, d, J = 6.2 Hz), 2.90 (3H, s), 5.23-5.30 (1H, m), 7.26 (1H, s), 8.46 (1H, s). MS ^{m}/z: 239 (M+1).

(d) Ácido 1-(3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il) piperidin-4-carboxílico

Isopropil 6-cloro-5-ciano-2-metilnicotinato (25.000 g, 104.75 mmol), ácido piperidin-4-carboxílico (14.205 g, 109.98 mmol) y DIPEA (d 0.742) (54.735 mL/314.24 mmol) se suspendieron en EtOH (200 mL) y se calentaron a reflujo durante 1 hora. La mezcla de reacción se enfrió a temperatura de la sala y se agregó gota a gota a $KHSO_4$ (71.316 g, 523.74 mmol) en agua (2000 mL). Los sólidos se recogieron por filtración y se secaron bajo vacío para proporcionar ácido 1-(3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 35 g (100%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (6H, d, J = 6.2 Hz), 1.81-1.93 (2H, m), 2.04-2.12 (2H, m), 2.67-2.74 (4H, m), 3.26-3.36 (2H, m), 4.53-4.62 (2H, m), 5.15-5.23 (1H, m), 8.32 (1H, s). MS $^m/_z$: 332 (M+1).

(e) Isopropil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil} piperidin-1-il)-5-ciano-2-metilnicotínico

Ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (30.00 g, 90.534 mmol), EDCI (26.03 g, 135.80 mmol), 1-fenilmetanosulfonamida (20.15 g, 117.69 mmol), HOBt (13.46g, 99.59 mmol) y DIPEA (47.308 mL, 271.60 mmol) se suspendieron en DCM (400 mL) y se agitaron durante 5 minutos hasta que se tornaron homogéneos. A continuación, la mezcla de reacción se hizo refluir durante 4 horas. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. La mezcla cruda de reacción se disolvió en EtOH (300 mL) y se agregó gota a gota a una solución rápidamente agitada de $KHSO_4$ (61.64 g, 452.67 mmol) en agua (3000 mL). El producto se recogió por filtración, se lavó con agua (3 x 400 mL) y se secó bajo vacío (44.00 g del producto seco). El producto seco se suspendió en alcohol isopropílico (2000 mL) y se agitó y se calentó a 50 °C durante 2 horas. El compuesto se aisló por filtración y se secó bajo alto vacío para proporcionar isopropil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 37.41 g (85%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (6H, d, J = 6.2 Hz), 1.74-1.90 (4H, m), 2.37-2.45 (1H, m), 2.73 (3H, s), 3.10-3.17 (2H, m), 4.63-4.67 (4H, m), 5.17-5.23 (1H, m), 7.33-7.42 (5H, m), 7.48 (1H, br s), 8.33 (1H, s). MS $^m/_z$: 485 (M+1).

La forma cristalina obtenida de caracterizó por la presencia, en mediciones de difracción de rayos X en polvo (XRPD), de picos a alrededor de valores 2-theta e intensidad relativa detallados en la siguiente Tabla 2.

Etiqueta del Pico	Ángulo (2-Theta, °)	Intensidad Relativa (%)
a	4.945	100.0
b	7.142	3.4
c	9.337	26.8
d	9.863	15.9
e	10.324	18.1
f	12.960	2.9
g	13.398	17.6
h	14.327	60.9
i	14.800	4.1

j	17.096	4.6
k	18.344	6.5
l	18.668	5.0
m	19.094	9.6
n	19.800	5.2
o	20.130	15.1
p	20.674	20.2
q	21.073	7.3
r	21.865	25.6
s	22.563	7.8
t	23.033	18.4
u	23.849	13.7
v	24.209	6.4
x	24.789	17.9
y	25.458	6.1
z	26.055	5.0
aa	26.390	4.3
ab	27.072	6.3
ac	27.718	4.8
ad	28.721	9.8
af	29.783	10.5
ag	30.260	4.8
y	25.458	6.1
z	26.055	5.0
aa	26.390	4.3
ab	27.072	6.3
ac	27.718	4.8
ad	28.721	9.8
af	29.783	10.5
ag	30.260	4.8
ah	30.840	4.8
ai	31.250	4.3
ak	34.511	4.3
al	36.014	4.4
am	37.174	4.1
an	37.855	3.5
ao	41.783	3.2
ap	43.320	4.9
aq	44.472	3.8
ar	45.346	3.1

Tabla 2: Picos XRPD para la Forma **I** de **etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico**

Ejemplo 40

Etil éster de ácido 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino} carbonil)piperidin-1-il]-2-metilnicotínico y [(4-cianobencil)sulfonil]({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il}carbonil) azanida de sodio

(a) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico

Etil 6-cloro-5-ciano-2-metilnicotinato (3.00g, 13.35 mmol), ácido piperidin-4-carboxílico (1.897g, 14.69 mmol), y TEA (2.703 g, 26.71 mmol) se mezclaron y la mezcla se hizo refluir durante 10 minutos. LC/MS mostró la conversión completa. La mezcla de reacción se evaporó, se agregó agua/EtOAc 1:1 (100 mL) y la fase acuosa se acidificó a pH3. La fase EtOAc se separó y la fase acuosa se extrajo con EtOAc adicional (40 mL). Las fases orgánicas se combinaron se secaron (Na_2SO_4), se filtraron y se evaporaron para producir 3.8 g de un material crudo.

Purificación con HPLC preparativa a pH=7 (0.1M NH_4OAC/CH_3CN) con el cambio subsiguiente a pH=3 proporcionó el producto puro. Rendimiento: 1.9 g (45%).

^1H NMR 400 MHZ, $CDCl_3$): δ 1.38 (t, J = 7.1 Hz, 3H), 1.94-1.82 (m, 2H), 2.13-2.05 (m, 2H), 2.75-2.66 (m, 5H), 3.37-3.27 (m, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.63-4.55 (m, 2H), 8.36 (s, 1H). MS $^m/_z$: 318 (M+1).

(b) Etil éster de ácido 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino} carbonil)piperidin-1-il]-2-metilnicotínico y [(4-cianobencil)sulfonil]({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il}carbonil) azanida de sodio

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.253 g, 0.8 mmol), 1-(4-cianofenil) metanosulfonamida (0.188 g, 0.96 mmol) y HATU (0.425 g, 1.12 mmol) se disolvieron en DMF y se agregó TEA (0.161 g, 1.6 mmol). Luego de 30 minutos más, se agregó DBU (0.243 g, 1.6 mmol) y la reacción se agitó a temperatura de la sala de

un día para otro. La mezcla de reacción se evaporó a sequedad y el residuo se repartió en porciones entre EtOAc (40 mL) y agua (40 mL). La fase orgánica se separó, se secó (Na_2SO_4), se filtró y se evaporó para producir un aceite amarillo. Purificación por HPLC preparativa - (Kromasil C8 10uM, 50x300mm, 100mL/minuto, pH=7) proporcionó 0.091 g de etil éster de ácido 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotínico puro como un sólido blanco. Este sólido se diluyó en CH_3CN (6 mL) y 0,1 M NaOH (1,9 mL) y se congeló en seco para proporcionar [(4-cianobencil)sulfonil]({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il}carbonil)azanida de sodio como un sólido blanco. Rendimiento: 0.101 g (24%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.2 Hz, 3H), 1.64-1.52 (m, 2H), 1.84-1.76 (m, 2H), 2.30-2.20 (m, 1H), 2.65 (s, 3H), 3.25-3.16 (m, 2H), 4.30-4.22 (q, J = 7.2 Hz, 2H), 4.36 (s, 2H), 4.48-4.40 (m, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 8.32 (s, 1H). MS $^m/_z$: 496 (M+1).

Ejemplo 41

Etil éster de ácido 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil) piperidin-1-il]-5-ciano-2-metilnicotínico y [(4-clorobencil)sulfonil]({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il}carbonil) azanida de sodio

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.250 g, 0.79 mmol), 1-(4-clorofenil) metanosulfonamida (0.0.194 g, 0.94 mmol) y HATU (0.419 g, 1.10 mmol) se disolvieron en DMF (5 mL), y se agregó TEA (0.161 g, 1.60 mmol). Luego de 30 minutos más, se agregó BEMP (0.432 g, 1.58 mmol) y la reacción se agitó a temperatura de la sala de un día para otro. La mezcla de reacción se evaporó a sequedad y el residuo se repartió en porciones entre EtOAc (30 mL) y agua (40 mL). Las fases se separaron y la fase acuosa se extrajo con EtOAc (30 mL). La fase orgánica combinada se separó, se secó (Na_2SO_4), se filtró y se evaporó para producir un aceite. La purificación en HPLC preparativa (Kromasil C8 10uM, 50x300mm, 100mL/minuto, pH=7)

proporcionó 0.101 g del etil éster de ácido 6-[4-({[(4-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotínico puro como un sólido blanco. Este sólido se disolvió en CH_3CN (6 mL) y 0,1 M NaOH (2.5 mL) y se secó por congelamiento para proporcionar [(4-clorobencil)sulfonil]({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il}carbonil)azanida de sodio, 101mg, como un sólido blanco. Rendimiento: 0.118 g (28%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.2 Hz, 3H), 1.66-1.53 (m, 2H), 1.85-1.76 (m, 2H), 2.32-2.22 (m, 1H), 2.65 (s, 3H), 3.25-3.16 (m, 2H), 4.30-4.22 (m, 4H), 4.49-4.41 (m, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 8.32 (s, 1H). MS $^m/_z$: 505 (M+1).

Ejemplo 42

Etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico

Una solución de etil 6-cloro-5-ciano-2-metilnicotinato (47.5 g, 211 mmol) y trietilamina (58.36 g, 577 mmol) en EtOH (314 ml) se agregó a una mezcla agitada de N-(bencilsulfonil)piperidin-4-carboxamida (53.55 g, 189.7 mmol, véase Ejemplo 31(b)) y EtOH (100 ml) a temperatura de la sala, y la mezcla se calentó a 100 °C (temperatura del baño, 20-100 °C durante 40 minutos, 100 °C 15 minutos, luego se enfrió a temperatura de la sala) durante 15 minutos. Una solución de $KHSO_4$ (142.93 g en 900 mL agua) se agregó para hacer que el producto se precipitara. El precipitado se extrajo completamente por filtración y se lavó con agua (2 x 250 mL) para producir 87 g de un producto crudo (84% puro). El producto crudo se suspendió en 50% EtOH (1200 mL) y se calentó a 50°C (temperatura del baño) durante 2 horas y 45 minutos, seguido por agitación de un día para otro a temperatura de la sala. La filtración proporcionó un producto crudo, el cual se lavó posteriormente agitando con 25% EtOH (1600 mL) a 50 °C durante 2 horas, seguido por 20% EtOH (1000 mL) a 50 °C durante 2 horas. (Un intento de purificar el material empleando una solución 50% EtOH/agua no tuvo éxito porque disolvió demasiada cantidad del producto). El sólido obtenido luego

o	24.878	5.0
p	25.459	6.0
q	25.762	24.3
r	25.821	12.5
s	27.298	3.7
t	27.736	4.4
u	34.301	4.2
v	41.444	4.4

Tabla 3: Picos XRPD para la Forma **I** de etil éster de ácido 6-(4-{[bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico

Etiqueta del Pico	Ángulo (2-Theta, °)	Intensidad Relativa (%)
A	3.530	100.0
B	7.097	12.7
C	13.363	5.6
D	10.782	2.4
E	14.038	3.0
F	14.762	3.6
G	17.849	2.8
H	18.332	8.9
I	18.596	6.0
J	19.601	4.2
K	20.733	3.4
L	21.500	5.6
M	21.674	7.0
N	23.178	3.7
O	25.057	3.1
P	26.256	3.6
Q	26.738	2.9
R	33.755	2.5
S	41.031	2.9

Tabla 4: Picos XRPD para la Forma **II** de etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico

Las formas cristalinas pueden caracterizarse aún más por la presencia de una o más de las propiedades adicionales enumeradas a continuación:

0.057 mmol). Se continuó la agitación a temperatura de la sala durante 20 horas. La purificación realizada mediante HPLC preparativa proporcionó el compuesto del título. Rendimiento: 0.014 g (46%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (t, J = 7.5 Hz, 3H), 1.66-1.54 (m, 2H), 1.84-1.77 (m, 2H), 2.29-2.20 (m, 1H), 2.77-2.70 (m, 5H), 3.21-3.12 (m, 2H), 4.40-4.32 (m, 2H), 4.72 (s, 2H), 7.01 (s, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 8.31 (s, 1H). MS $^m/_z$: 535 (M+1).

Ejemplo 44

***N*-(Bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]azetidin-3-carboxamida**

(a) Ácido 1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il] azetidin-3-carboxílico

2-Cloro-5-(5-etil-1,3-oxazol-2-il)-6-metilnicotinonitrilo (0.028 g, 0.11 mmol) se disolvió en EtOH seco (2 mL) en un frasco de proceso Smith. Se agregaron ácido azetidin-3-carboxílico (0.023 g, 0.23 mmol) y TEA (0.114 g, 1.13 mmol), y el frasco sellado se calentó en un horno microondas, calentamiento de nodo simple, a 120 °C durante 20 minutos. LC/MS mostró conversión completa. La mezcla de reacción se evaporó. 1M HCl (2 mL) se agregó. La mezcla se extrajo con DCM (3x2 mL) empleando un separador de fase. La fase orgánica se combinó, se secó con sulfato de sodio y se evaporó. Esto produjo 0.033 g del producto crudo. La purificación mediante cromatografía instantánea en gel de sílice con DCM/MeOH 39:1 + 1% ácido fórmico como eluyente proporcionó el producto puro. Rendimiento: 0.026 g (74%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 1.5 Hz, 3H), 2.80-2.70 (m, 5H), 3.70-3.57 (m, 1H), 4.68-4.57 (m, 4H), 6.88 (br s, 1H), 8.20 (s, 1H)

MS $^m/_z$: 313 (M+1).

(b) N-(Bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]azetidin-3-carboxamida

Ácido 1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.012 g, 0.038 mmol) se disolvió en DMF (0.5 mL). Se agregaron HATU (0.018 g, 0.046 mmol) y DIPEA (0.025 g, 0.19 mmol), y la mezcla de reacción se agitó a temperatura de la sala durante 30 minutos antes de agregar 1-fenilmetanosulfonamida (0.008 g, 0.046 mmol). Se continuó la agitación a temperatura de la sala durante 18 horas. De acuerdo con LC/MS no se había formado producto en este punto. Se agregaron EDCI ((0.007 g, 0.038 mmol) y HOBt (0.008 g, 0.058 mmol), y se continuó la agitación a temperatura de la sala durante 28 horas más. Se agregó más 1-fenilmetanosulfonamida (0.005 g, 0.029 mmol) y se continuó la agitación a temperatura de la sala durante el fin de semana (64 horas). De acuerdo con LC/MS la reacción se había completado en este punto. La purificación mediante HPLC preparativa proporcionó el producto puro. Rendimiento: 0.0005 g (5%).

^{1}H NMR (400 MHz, CD_3Cl): δ 1.30 (t, J = 7.6 Hz, 3H), 2.74 (q, J = 7.6 Hz, 2H), 2.79 (s, 3H), 3.38-3.28 (m, 1H), 4.45-4.40 (m, 4H), 4.66 (s, 2H), 6.82 (s, 1H), 7.42-7.34 (m, 5H), 8.21 (s, 1H). MS $^m/_z$: 466 (M+1).

Ejemplo 45

***N*-[(4-Clorobencil)sulfonil]-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida**

Ácido 1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.026 g, 0.075 mmol) se disolvió en DMF (1 mL). Se agregaron HATU (0.019 g, 0.090 mmol) y DIPEA (0.048 g, 0.38 mmol), y la mezcla de reacción se agitó a temperatura de la sala durante 15 minutos antes de agregar 1-(4-clorofenil)metanosulfonamida (0.019 g, 0.090 mmol). Se continuó la agitación a temperatura de la sala durante 27.5 horas. De acuerdo con LC/MS la reacción estaba incompleta en este punto. Se agregaron más HATU (0.028 g, 0.075 mmol) y 1-(4-clorofenil)metanosulfonamida (0.014 g, 0.068 mmol), y se continuó la

agitación a temperatura de la sala durante 26 horas más. LC/MS mostró que la reacción estaba casi completa. La purificación mediante HPLC preparativa proporcionó el producto puro. Rendimiento: 0.008 g (18%).
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30-1.22 (t, J = 7.5 Hz, 3H), 1.74- 1.61 (m, 2H), 1.91- 1.82 (m, 2H), 2.64-2.55 (m, 1H), 2.80-2.71 (m, 5H), 3.18-3.08 (m, 2H), 4.52-4.44 (m, 2H), 4.74 (s, 2H), 7.04 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 8.35 (s, 1H), 11.65 (s, 1H). MS $^m/_z$: 528 (M+1).

Ejemplo 46

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonil aminocarbonil-azetidin-1-il)-nicotínico

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (20.00 g, 69.14 mmol), EDCI (19.88 g, 103.7 mmol), 1-fenil-metanosulfonamida (15.39 g, 89.188 mmol), HOBt (10.276 g, 76.049 mmol) y DIPEA (36.127 mL, 207.41 mmol) se suspendieron en DCM (500 mL) y se agitaron a temperatura de la sala durante 5 minutos hasta que se tornaron homogéneos. A continuación la mezcla de reacción se hizo refluir durante 3 horas. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. La mezcla cruda de reacción se disolvió en EtOH (400 mL) y se agregó gota a gota a una solución rápidamente agitada de $KHSO_4$ (47.07 g, 345.68 mmol) en agua (4000 mL). El producto se recogió por filtración, se lavó con agua (3 x 500 mL) y se secó bajo vacío (30.61 g de producto seco). El producto seco se suspendió en EtOH (1500 mL) y se agitó a 50 °C durante 1 hora. El compuesto se aisló mediante filtración y se secó bajo alto vacío para proporcionar el material deseado como cristales. Rendimiento: 27.65 g (90%).
^{1}H NMR (400 MHz, DMSO-d_6) d 1.23 (t, J = 7.2 Hz, 3H), 2.57 (s, 3H), 3.43 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.23 (t, J = 7.1 Hz, 2H), 4.34 (t, J = 8.9 Hz, 2H), 4.68 (s, 2H), 7.29 (m, 5H), 8.33 (s, 1H), 11.75 (s, 1H). MS $^m/_z$: 443 (M+1).

Los cristales se caracterizaron por la presencia, en mediciones de difracción de rayos X en polvo (XRPD), de picos de alrededor de los valores 2-theta e intensidad relativa, detallados en la siguiente Tabla 5.

Etiqueta de Pico	Ángulo (2-Theta, °)	Intensidad Relativa (%)
a	5.388	100.0
b	7.293	12.0
c	10.049	6.2
d	10.796	28.8
e	13.263	4.1
f	13.949	16.4
g	14.597	21.8
h	16.177	3.1
i	17.691	3.8
j	18.888	5.0
k	20.053	10.7
l	20.477	12.6
m	20.990	15.9
n	21.608	26.7
o	22.577	9.1
P	23.991	16.0
q	24.872	9.6
r	26.203	7.9
s	26.761	7.7
t	27.188	11.8
u	31.221	4.9
v	34.030	5.6

Tabla 5: Picos XRPD para la Forma **I** de etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico

Ejemplo 47

Etil 5-ciano-6-{3-[({[3-(4-metoxifenoxi)propil]sulfonil}amino)carbonil] azetidin-1-il}-2-metilnicotinato

Preparado de acuerdo con el método A usando 3-(4-metoxifenoxi)propano-1-sulfonamida (0.105 g crudo, 0.37 mmol). Rendimiento: 0.041 g (32%). ^{1}H NMR (400 MHz, DMSO d_6) d 1.23 (t, J = 7.1 Hz, 3H), 2.03 (quintete, J = 6.6 Hz, 2H), 2.54 (s, 3H), 3.59 (s, 3H), 3.6 - 3.4 (m, 3H superpuesto por

agua), 3.94 (t, J = 6.0 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.27 (m, 2H), 4.38 (t, J = 8.6 Hz, 2H), 6.75 (m, 4H), 8.21 (s, 1H). MS $^{m}/_{z}$: 517 (M+1).

Ejemplo 48

Etil 4-amino-6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloronicotinato

(a) Etil 4-amino-6-(3-(*terc*-butoxicarbonil)azetidin-1-il)-5-cloronicotinato

Etil 4-amino-5,6-dicloronicotinato (0.560 g, 2.38 mmol) se disolvió en DMA (5 mL), y se agregaron *terc*-butil azetidin-3-carboxilato (0.65 g, 4.1 mmol) y DIPEA (1.2 mL, 7.1 mmol). La reacción se calentó a 90 °C. Después de 4 horas, se agregaron más *terc*-butil azetidin-3-carboxilato (0.32 g, 2.0 mmol) y DIPEA (1.0 mL, 5.9 mmol) y se continuó el calentamiento. Después de 2 horas se agregaron más *terc*-butil azetidin-3-carboxilato (0.45 g, 2.9 mmol) y DIPEA (1.0 mL, 5.9 mmol). La reacción se calentó 1.5 horas más y luego la reacción se enfrió y se concentró bajo presión reducida. El residuo se disolvió en EtOAc (150 mL) y se lavó con NH_4Cl saturado (2 x 75 mL), salmuera y se secó ($MgSO_4$). La solución se concentró luego bajo presión reducida, y el producto crudo se purificó con cromatografía instantánea (DCM a 5% EtOAc/DCM) para proporcionar etil 4-amino-6-(3-(*terc*-butoxicarbonil)azetidin-1-il)-5-cloronicotinato como un sólido. Rendimiento: 0.38 g (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (3H, t, J = 7.1 Hz), 1.48 (9H, s), 3.34-3.42 (1H, m), 4.30 (2H, q, J = 7.1 Hz), 4.40-4.48 (4H, m), 8.53 (1H, s). MS $^{m}/_{z}$: 356 (M+1).

(b) Clorhidrato de ácido 1-(4-amino-3-cloro-5-(etoxicarbonil)piridin-2-il)azetidin-3-carboxílico

Etil 6-(3-(*terc*-butoxicarbonil)azetidin-1-il)-4-amino-5-cloronicotinato (0.37 g, 1.0 mmol) se disolvió en una solución de 4M HCl en dioxano (5 mL). Luego de 14 horas a temperatura de la sala y la reacción se concentró bajo

presión reducida y se destiló a temperatura fija con DCM y EtOAc para proporcionar clorhidrato de ácido 1-(4-amino-3-cloro-5-(etoxicarbonil) piridin-2-il)azetidin-3-carboxílico, el cual se utilizó sin purificación adicional. Rendimiento: 0.35 g, (100%).

(c) Etil 4-amino-6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloronicotinato

Clorhidrato de ácido 1-(4-amino-3-cloro-5-(etoxicarbonil)piridin-2-il)azetidin-3-carboxílico (0.077 g, 0.23 mmol) se combinó con EDCI (0.057 g, 0.30 mmol) y HOBt (0.040 g, 0.30 mmol) en DCM (4 mL). A continuación se agregó fenilmetanosulfonamida (0.055 g, 0.32 mmol), seguida por DIPEA (0.24 mL, 1.4 mmol). La reacción se dejó agitar 14 horas. La reacción se repartió entonces en porciones entre EtOAc (75 mL) y solución de NH_4Cl (20 mL). El orgánico se lavó con NH_4Cl (20 mL) y luego salmuera (20 mL). La fase orgánica se secó ($MgSO_4$) y se concentró. La mezcla cruda de reacción se purificó mediante cromatografía de columna (30 a 50% EtOAc/hexanos, luego se agregó 0.5% HOAc). Etil 4-amino-6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloronicotinato se aisló como un sólido. Rendimiento: 0.070 g (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 3.19-3.26 (1H, m), 4.28-4.38 (6H, m), 4.70 (2H, s), 7.38-7.40 (5H, m), 8.53 (1H, s). MS $^m/_z$: 453 (M+1).

Ejemplo 49

Etil 5-ciano-2-metil-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.058 g, 0.2 mmol) se disolvió en DMF (1 mL) y HATU (0.099 g, 0.26 mmol), DPEA (0.170 mL, 1 mmol), y se agregó 1-(3-metilfenil)metanosulfonamida (0.037 g, 0.2 mmol) a temperatura de la sala y la reacción se agitó durante 30 horas. El disolvente se retiró *in vacuo* y el residuo se purificó mediante HPLC preparativa (Kromasil C8 10 μM ,

columna 20 x 100 mm, caudal: 30 mL/minuto usando una gradiente de 0.1 M NH_4OAc y CH_3CN) para proporcionar el producto puro. Rendimiento: 0.019 g (15%).

^1H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.1 Hz, 3H), 2.33 (s, 3H), 2.65 (s, 3H), 3.53- 3.62 (m, 1H), 4.21-4.34 (m, 4H), 4.39-4.47 (m, 2H), 4.72 (s, 2H), 7.13-7.32 (m, 4H), 8.33 (s, 1H), 11.81 (br s, 1H). MS $^m/_z$: 457 (M+1).

Ejemplo 50

2,2-Dimetilpropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

(a) Etil 6-(4-(*terc*-butoxicarbonil)piperidin-1-il)-5-ciano-2-metilnicotinato

Una solución de etil 6-cloro-5-ciano-2-metilnicotinato (6.00 g, 26.7 mmol), clorhidrato de *terc*-butil piperidin-4-carboxilato (6.51, 29.4 mmol) y DIPEA (23.3 mL, 134 mmol) en DMA (50 mL) se calentó a 80 °C durante 2 horas. Luego de enfriar a temperatura de la sala, la mezcla de reacción se diluyó con EtOAc (300 mL), se lavó con NH_4Cl saturado (4 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$), se pasó a través de gel de sílice y se concentró. Cromatografía instantánea produjo etil 6-(4-(*terc*-butoxicarbonil)piperidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 8.85 g (89%).

^1H NMR (400 MHz, $CDCl_3$): δ ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.45 (9H, s), 1.75-1.84 (2H, m), 1.99-2.03 (2H, m), 2.49-2.57 (1H, m), 2.72 (3H, s), 3.24-3.31 (2H, m), 4.31 (2H, q, J = 7.1 Hz), 4.55-4.60 (2H, m), 8.34 (1H, s). MS $^m/_z$: 374 (M+1).

(b) Ácido 6-(4-(*terc*-butoxicarbonil)piperidin-1-il)-5-ciano-2-metilnicotínico

A una solución de etil 6-(4-(*terc*-butoxicarbonil)piperidin-1-il)-5-ciano-2-metilnicotinato (6.65 g, 17.8 mmol) en THF 50 mL se agregó LiOH acuoso

(1.0 M, 107 mL, 107 mmol) y la mezcla se calentó a reflujo durante 5 horas. Luego de enfriar a temperatura de la sala, la reacción se acidificó a pH 3.5 con 2 M HCl y se extrajo en EtOAc (4 x 50 mL). Los extractos orgánicos se lavaron con salmuera, se secaron ($MgSO_4$), se pasaron a través de gel de sílice y se concentraron. Cromatografía instantánea (20% EtOAc/hexanos con 1% HOAc) proporcionó ácido 6-(4-(*terc*-butoxicarbonil)piperidin-1-il)-5-ciano-2-metilnicotínico como un sólido. Rendimiento: 1.8 g (29%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (9H, s), 1.53-1.63 (92H, m), 1.90-1.94 (2H, m), 2.55- 2.60 (1H, m), 2.64 (3H, s), 3.21-3.28 (2H, m), 4.40-4.44 (2H, m), 8.30 (1H, s), 12.91 (1H, br s). MS $^m/_z$: 350 (M+1).

(c) 2,2-Dimetilpropil 6-[4-(*terc*-butoxicarbonil)piperidin-1-il]-5-ciano-2-metilnicotinato

Una solución de ácido 6-(4-(*terc*-butoxicarbonil)piperidin-1-il)-5-ciano-2-metilnicotínico (0.845 g, 2.45 mmol), alcohol neopentílico (1.30 g, 14.7 mmol), EDCI (2.11 g, 11.0 mmol), HOBt (0.496 g, 3.67 mmol) y DIPEA (0.852 mL, 4.89 mmol) se calentó a 80 °C durante 2 días. La mezcla de reacción se diluyó con EtOAc (50 mL), se lavó con NH_4Cl saturado (3 x 30 mL), salmuera, se secó ($MgSO_4$), se pasó a través de gel de sílice y se concentró. Cromatografía instantánea (3% EtOAc/hexanos) produjo 2,2-dimetilpropil 6-[4-(*terc*-butoxicarbonil)piperidin-1-il]-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 1.02 g (41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (9H, s), 1.46 (9H, s), 1.76-1.85 (2H, m), 2.00-2.03 (2H, m), 2.49-2.57 (1H, m), 2.73 (3H, M), 3.25-3.31 (2H, m), 3.96 (2H, s), 4.56-4.60 (2H, m), 8.32 (1H, s). MS $^m/_z$: 416 (M+1).

(d) Ácido 1-{3-ciano-5-[(2,2-dimetilpropoxi)carbonil]-6-metilpiridin-2-il} piperidin-4-carboxílico

A una solución de 2,2-dimetilpropil 6-[4-*terc*-butoxicarbonil)piperidin-1-il]-5-ciano-1-metilnicotinato (0.415 g, 0.999 mmol) en DCM (10 mL) a 0 °C se agregó TFA (10 mL) y la mezcla de reacción se agitó durante 2 horas.

La concentración produjo ácido 1-{3-ciano-5-[(2,2-dimetilpropoxi) carbonil]-6-metilpiridin-2-il}piperidin-4-carboxílico, el cual se utilizó crudo asumiendo una conversión del 100%. MS $^{m}/_{z}$: 513 (M+1).

(e) 2,2-Dimetilpropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2- metilnicotinato

Una solución de ácido 1-{3-ciano-5-[(2,2-dimetilpropoxi)carbonil]-6-metilpiridin-2-il}piperidin-4-carboxílico (0.120 g, 0.334 mmol), EDCI (0.0832 g, 0.434 mmol) y DIPEA (0.291 mL, 1.67 mmol) en DCM (3 mL) se agitó a temperatura de la sala durante 30 minutos. Se agregó fenilmetanosulfonamida (0.0686 g, 0.401 mmol) y la agitación se continuó durante 18 horas. Se agregaron más EDCI (0.0832 g, 0.434 mmol) y fenilmetanosulfonamida (0.0686 g, 0.401 mmol) y la mezcla de reacción se agitó durante 3 días, se diluyó con EtOAc (50 mL), se lavó con NH_4Cl saturada (3 x 30 mL), salmuera, se secó ($MgSO_4$) y se concentró. Cromatografía instantánea (1:4 EtOAc/hexanos con 1% HOAc), seguida por purificación de HPLC de fase inversa proporcionó 2,2-dimetilpropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.0175 g (10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (9H, s), 1.78-1.91 (4H, m), 2.83-2.46 (1H, m), 2.74 (3H, s), 3.11-3.18 (2H, s), 3.97 (2H, s), 4.65-4.70 (4H, m), 7.34-7.35 (2H, m), 7.39-7.41 (3H, m), 8.34 (1H, s). MS $^{m}/_{z}$: 513 (M+1).

Ejemplo 51

Etil 5-ciano-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato

Cloruro de tionilo (0.119 g, 1 mmol) se agregó a una solución de 1-[3-ácido ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (0.058 g, 0.2 mmol) en DCM (1 mL) a 0 °C, y la mezcla de reacción se dejó alcanzar la temperatura de la sala y se agitó durante 30 minutos. El DCM y el exceso de cloruro de tionilo se evaporó (el residuo se re-disolvió en DCM (1 mL) y se evaporó, esto se repitió una sola vez) y el residuo se disolvió en

piridina a 0 °C seguida por la adición 1-(4-metilfenil)metanosulfonamida (0.044 g, 0.24 mmol). Después de agitar durante 2 horas a temperatura de la sala, se agregó DMAP (unos cuantos cristales) y la agitación se continuó durante 19 horas. Se agregó BEMP (0.055 g, 0.2 mmol) y la agitación se continuó durante 22 horas a temperatura de la sala. LC/MS mostró que sólo los materiales de partida estaban presentes. Se agregaron HATU (0.152 g, 0.4 mmol) y DIPEA (0.259g, 2 mmol) a la mezcla a temperatura de la sala y la agitación se continuó durante 20 horas a temperatura de la sala. El disolvente se retiró *in vacuo* y el residuo se purificó mediante HPLC preparativa (Kromasil C8 10 μM, columna 20 x 100 mm, caudal: 30 mL/minuto empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) para producir el producto puro. Rendimiento: 0.019 g (15%).

^1H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, J = 7.0 Hz, 3H), 2.32 (s, 3H), 2.66 (s, 3H), 3.51- 3.60 (m, 1H), 4.20-4.37 (m, 4H), 4.38-4.47 (m, 2H), 4.70 (s, 2H), 7.17-7.28 (m, 4H), 8.34 (s, 1H), 11.77 (br s, 1H). MS $^m/_z$: 457 (M+1).

Ejemplo 52

Etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato y ({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il}carbonil)[(4-fluorobencil)sulfonil]azanida de sodio

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.350 g, 1.10 mmol), EDCI (0.274 g, 1.43 mmol)), 1-(4-fluorofenil)metanosulfonamida (0.271 g, 1.43 mmol) y HOBt (0.194 g, 1.43 mmol) se suspendieron en DCM (8 mL), y se agregó DIPEA (0.713 g, 5.51 mmol) a la suspensión. La reacción se volvió homogénea después de 30 minutos y la agitación se continuó de un día para otro. El disolvente se retiró *in vacuo* y el residuo se disolvió en EtOAc(20 mL). La fase orgánica se lavó con 0.5 M $KHSO_4$ (5 mL), agua (5 mL) y se evaporó para producir un producto crudo. La purificación mediante HPLC preparativa (Kromasil C8) proporcionó 0.429 g de etil 5-ciano-6-[4-({[(4- fluorobencil)sulfonil] amino}carbonil)piperidin-1-il]-2-metilnicotinato como un sólido blanco. ^1H

NMR (400 MHz, DMSO-d_6) δ 1.30 (t, J = 7.2 Hz, 3H), 1.56-1.69 (m, 2H), 1.80-1.88 (m, 2H), 2.57 (m, 1H), 2.64 (s, 3H), 3.13 (m, 2H), 4.24 (q, J =7.2 Hz, 2H), 4.53 (m, 2H), 4.68 (s, 2H), 7.20-7.27 (m, 2H), 7.30-7.35 (m, 2H), 8.33 (s, 1H), 11.60 (br s, 1H). Este sólido se disolvió en CH_3CN (3 mL), 0.1 M NaOH(8.5 mL) y finalmente se secaron por congelamiento para producir ({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il} carbonil)[(4-fluorobencil)sulfonil]azamida de sodio como un sólido blanco. Rendimiento: 0.444 g (76%).

Ejemplo 53

Etil 6-[4-({[(3-bromobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato

HATU (0.205 g, 0.54 mmol) y DIPEA (0.194 g, 1.5 mmol) se agregaron a una solución agitada de ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.095 g, 0.30 mmol) en DMF (1.5 mL) a temperatura de la sala, seguido por 1-(3-bromofenil)metanosulfonamida (0.090 g, 0.36 mmol), y la reacción se agitó durante 16 horas. El disolvente se retiró y el producto crudo se purificó mediante HPLC preparativa (Kromasil C8, 250 mm x 50 mm diámetro interno, caudal 50 mL/minuto, empleando una gradiente lineal de 0:1 M NH_4OAc/CH_3CN 95/5 a 0/100 durante 40 minutos. Rendimiento: 0.035 g (21%).

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.32 (t, J = 7.0 Hz, 3H), 1.58-1.74 (m, 2H), 1.80-1.90 (m, 2H), 2.00-2.15 (m, 1H), 2.66 (s, 3H), 3.10-3.22 (m, 2H), 4.27 (q, J = 7.0 Hz, 2H), 4.51-4.61 (m, 2H), 4.75 (s, 2H), 7.29-7.35 (m, 1H), 7.37-7.44 (m, 1H), 7.47-7.51 (m, 1H), 7.60-7.66 (m, 1H), 8.36 (s, 1H), 11.68 (br s, 1H). MS $^m/_z$: 550 (M+1).

Ejemplo 54

Ciclopropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

(a) Bencil 2-[(dimetilamino)metilene]-3-oxobutanoato

Bencil 3-oxobutanoato (82 mL, 475mmol) se agitó a temperatura de la sala y se agregó 1,1-dimetoxi-N,N-dimetilmetanamina (76 mL, 570 mmol) gota a gota. La mezcla de reacción se dejó agitar a temperatura de la sala de un día para otro. La mezcla de reacción se concentró bajo vacío y luego se destiló a temperatura fija con tolueno (3 x 200 mL) y se puso bajo alto vacío para proporcionar bencil 2-[(dimetilamino)metilen]-3-oxobutanoato como un aceite, el cual se utilizó sin purificación adicional. Rendimiento: 117 g (100%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, s), 3.02 (6H, br s), 5.22 (2H, s), 7.29-7.43 (5H, m), 7.70 (1H, s).

(b) Bencil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

NaH (19.9 g, 498 mmol) se agregó una solución agitada a temperatura de la sala de 2-cianoacetamida (39.9 g, 475 mmol) en THF (1 L). La mezcla de reacción se agitó a temperatura de la sala hasta que cesó la evolución de gas. Se agregó en porciones bencil 2-[(dimetilamino)metilen]-3-oxobutanoato (117.4 g, 474.7 mmol) y la mezcla de reacción se agitó a temperatura de la sala de un día para otro. Se agregó 1N HCl y el sistema se agitó a temperatura de la sala durante 1 hora y, seguidamente, la mezcla de reacción se diluyó con EtOAc y se extrajo. Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar bencil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 111 g (88%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.63 (3H, s), 5.29 (2H, s), 7.34-7.47 (5H, m), 8.72 (1H, s), 12.82 (1H, s). MS $^m/_z$: 267 (M-1).

(c) Ácido 6-cloro-5-ciano-2metilnicotínico

Bencil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato se suspendió en $POCl_3$ (43.44 mL, 474.5 mmol) y se calentó a 100 °C de un día para otro. La mezcla de reacción se enfrió a temperatura de la sala y se virtió sobre hielo. El acuoso se neutralizó con NaHCO sólido y se extrajo en DCM. Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida

para proporcionar el material. Cromatografía instantánea (elución de gradiente 30 - 50% EtOAc / hexanos, 0.5% AcOH) produjo ácido 6-cloro-5-ciano-2-metilnicotínico crudo como un sólido. Rendimiento: 24.2 g (26%). ^{1}H NMR (400 MHz, CDCi): δ 3.00 (3H, s), 8.50 (1H, s). MS $^m/_z$: 195 (M-1).

(d) Cloruro de 6-cloro-5-ciano-2-metilnicotinoilo

Ácido 6-cloro-5-ciano-2-metilnicotínico (4.00 g, 20.4 mmol) y cloruro de oxalilo (2.66 mL, 30.5 mmol) se suspendieron en DCM (75 mL) y se calentaron a 80 °C durante 1 hora. La mezcla de reacción se concentró bajo presión reducida y se destiló a temperatura fija con hexanos y tolueno. La mezcla de reacción se concentró entonces bajo presión reducida para proporcionar el cloruro de 6-cloro-5-ciano-2-metilnicotinoilo crudo, el cual se utilizó sin purificación adicional.

(e) Ciclopropanol

Ciclopropanol preparado de acuerdo con la literatura: *J. Org. Chem.* 41(7), 1237-40, 1976. y *J. Org. Chem* 45(21), 4129-35, 1980.

e) Ciclopropil 6-cloro-5-ciano-2-metilnicotinato

Cloruro de 6-cloro-5-ciano-1-metilnicotinoilo (2.00 g, 9.30 mmol), ciclopropanol (0.54 mL, 9.30 mmol) y DIPEA (1.62 mL, 9.30 mmol) se suspendieron en DCM (40 mL) y se agitaron a temperatura de la sala durante 16 horas. Se agregó agua (40 mL) a la solución y se agitó durante 5 minutos. Las capas se separaron y los orgánicos se lavaron con agua (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (40% DCM en hexanos) proporcionó ciclopropil 6-cloro-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.500 g (23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85-0.92 (4H, m), 2.90 (3H, s), 4.38-4.45 (1H, m), 8.41 (1H, s).

(f) Ácido 1-(3-ciano-5-(ciclopropoxicarbonil)-6-metilpiridin-2-il) azetidin-3-carboxílico

Ciclopropil 6-cloro-5-ciano-2-metilnicotinato (0.084 g, 0.354 mmol), ácido 3-azetidincarboxílico (0.090 g, 0.887 mmol), y DIPEA (0.442 mL, 2.54 mmol), se suspendieron en EtOH (4 mL) y luego se hicieron refluir durante 1 hora. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. Se agregó EtOAc (50 mL) y la mezcla de reacción se lavó con NH_4Cl saturada (2 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo ácido 1-(3-ciano-5-(ciclopropoxicarbonil)-6-metilpiridin-2-il)azetidin-3-carboxílico como un sólido. Rendimiento: 0.180 g (71%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.83 (4H, m), 2.61 (3H, s), 3.50-3.60 (1H, m), 4.21-4.27 (1H, m), 4.31-4.39 (2H, m), 4.45-4.54 (2H, m), 8.26 (1H, s), 12.8 (1H, s).

(g) Ciclopropil 6-(3-(bencilsulfonilcarbamoil)azetidin-1-il)-5-ciano-2 - metilnicotinato

Ácido 1-(3-ciano-5-(ciclopropoxicarbonil)-6-metilpiridin-2-il)azetidin-3-carboxílico (0.165 g, 0.548 mmol), EDCI (0.157 g, 0.821 mmol), fenilmetanosulfonamida (0.113 g, 0.657 mmol), HOBt (0.081 g, 0.602 mmol) y DIPEA (0.286 mL, 1.64 mmol) se suspendieron en DCM (10 mL) y luego se hicieron refluir durante 3 horas. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. La mezcla cruda de reacción se disolvió en EPA (10 mL) y se agregó gota a gota a una solución rápidamente agitada de $KHSO_4$ (0.373 g, 2.74 mmol) en agua (100 mL). El producto se recogió por filtración, se lavó con agua (3 x 20 mL) y se secó bajo vacío. El producto crudo se suspendió en IPA (100 mL), se agitó y se calentó a 50 °C durante 1 hora. La solución se enfrió entonces a 0 °C durante 3 horas. El material se aisló mediante filtración y se secó bajo alto vacío para producir ciclopropil 6-(3-(bencilsulfonilcarbamoil)azetidin-

1-il)-5-ciano-2-metilnicotinato como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 0.146 g (53%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.83 (4H, m), 2.63 (3H, s), 3.52-3.59 (1H, m), 4.22-4.47 (5H, m), 4.75 (2H, s), 7.31-7.43 (5H, m), 8.28 (1H, s), 11.8 (1H, s). MS $^m/_z$: 455 (M+1).

Ejemplo 55

2,2,2-Trifluoroetil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

(a) 2,2,2-Trifluoroetil 6-cloro-5-ciano-2-metilnicotinato

Cloruro de de 6-cloro-5-ciano-2-metilnicotinoilo crudo (0.500 g, 2.32 mmol), 2,2,2-trifluoroetanol (1.69 mL, 23.2 mmol) y DIPEA (2.02 mL, 11.63 mmol) se suspendieron en DCM (10 mL) y se agitaron a temperatura de la sala hasta que se observó un consumo completo del material inicial por Análisis HPLC. La mezcla de reacción se diluyó con DCM y se lavó con $NaHCO_3$ saturado. Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (100% DCM) produjo 2,2,2-trifluoroetil 6-cloro-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.155 g (24%).

(b) 2,2,2-Trifluoroetil 6-(4-{[(bencilsulfonil)amino]carbonil} piperidin-1-il)-5-ciano-2-metilnicotinato

2,2,2-Trifluoroetil 6-cloro-5-ciano-2-metilnicotinato (0.057 g, 0.204 mmol), clorhidrato de N-(bencilsulfonil)piperidin-4-carboxamida (0.085 g, 0.266 mmol, véase Ejemplo 34(d)) y DIPEA (0.18 mL, 1.023 mmol) se suspendieron en DMF (5 mL) y se agitaron a temperatura de la sala durante 4 horas. La mezcla de reacción se agregó gota a gota a una solución agitada de $KHSO_4$ (0.195 g, 1.43 mmol) en agua (50 mL). El producto se recogió por filtración se secó bajo alto vacío para producir 2,2,2-trifluoroetil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.095 g (88%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.58-1.72 (2H, m), 1.81-1.91 (2H, m), 2.55-2.69 (4H, m), 3.13-3.24 (2H, m), 4.54-4.64 (2H, m), 4.70 (2H, s), 4.90-4.98 (2H, m), 7.26-7.33 (2H, m), 7.36-7.45 (3H, m), 8.34 (1H, s), 11.61 (1H, s). MS $^m/_z$: 525 (M+1).

Ejemplo 56

2,2,2-Trifluoroetil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato

(a) Ácido 1-(3-ciano-6-metil-5-((2,2,2-trifluoroetoxi)carbonil)piridin-2-il)azetidin-3-carboxílico

2,2,2-Trifluoroetil 6-cloro-5-ciano-2-metilnicotinato (0.155 g, 0.556 mmol), ácido azetidin-3-carboxílico (0.068 g, 0.67 mmol) y DIPEA (0.485 mL, 2.78 mmol) se suspendieron en EtOH (10 mL) y se calentaron a reflujo durante 1 hora. La mezcla de reacción se enfrió a temperatura de la sala y se agregó gota a gota a $KHSO_4$ (0.53 g, 3.89 mmol) en agua (100 mL). Los sólidos se recogieron por filtración y se secaron bajo vacío para proporcionar el material deseado crudo. Cromatografía instantánea (eluyente 30 - 50% EtOAc / hexanos 0.5% AcOH) produjo ácido 1-(3-ciano-6-metil-5-((2,2,2-trifluoroetoxi)carbonil)piridin-2-il)azetidin-3-carboxílico como un sólido. Rendimiento: 0.136 g (71%).

^{1}H NMR (400 MHz, $CDlC_3$): δ 2.72 (3H, s), 3.60-3.69 (1H, m), 4.58-4.70 (6H, m), 8.29 (1H, s). MS $^m/_z$: 344 (M+1).

(b) 2,2,2-Trifluoroetil 6-(3-{[(bencilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-metilnicotinato

Ácido 1-(3-ciano-6-metil-5-((2,2,2-trifluoroetoxi)carbonil)piridin-2-il) azetidin-3-carboxílico (0.068 g, 0.198 mmol), fenilmetanosulfonamida (0.044 g, 0.258 mmol), EDCI (0.057 g, 0.297 mmol), HOBt (0.029 g, 0.218 mmol) y DIPEA (0.10 mL, 0.59 mmol) se suspendieron en DCM (5 mL) y se calentaron a reflujo durante 4 horas. La mezcla de reacción se diluyó con DCM y se lavó con NH_4Cl saturado, y los orgánicos se secaron

($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (elución de gradiente 30 - 50% EtOAc / hexanos, 0.5% AcOH) produjo 2,2,2-trifluoroetil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.061 g (62%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.52-3.62 (1H, m), 4.28-4.38 (2H, m), 4.39-4.51 (2H, m), 4.76 (2H, s), 4.86-4.97 (2H, m), 7.30-7.43 (5H, m), 8.13 (1H, s), 11.83 (1H, s). MS $^m/_z$: 497 (M+1).

Ejemplo 57

2,2,2-Trifluoroetil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil) azetidin-1-il]-5-ciano-2-metilnicotinato

Ácido 1-(3-ciano-6-metil-5-((2,2,2-trifluoroetoxi)carbonil)piridin-2-il) azetidin-3-carboxílico (0.068 g, 0.198 mmol), (4-clorofenil) metanosulfonamida (0.053 g, 0.258 mmol), EDCI (0.057 g, 0.297 mmol), HOBt (0.0294 g, 0.218 mmol) y DIPEA (0.104 mL, 0.594 mmol) se suspendieron en DCM (5 mL) y se calentaron a reflujo durante 4 horas. La mezcla de reacción se diluyó con DCM y se lavó con NH_4Cl saturado, los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (elución de gradiente 30 - 50% EtOAc / hexanos, 0.5% AcOH) produjo 2,2,2-trifluoroetil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.067 g (64%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.54-3.64 (1H, m), 4.27-4.38 (2H, m), 4.41-4.52 (2H, m), 4.78 (2H, s), 4.85-4.97 (2H, m), 7.33-7.41 (2H, m), 7.42-7.50 (2H, m), 8.31 (1H, s), 11.85 (1H, s). MS $^m/_z$: 531 (M+1).

Ejemplo 58

Ciclopropil 6-(4-(bencilsulfonilcarbamoil)piperidin-1-il)-5-ciano-2-metilnicotinato

Ciclopropil 6-cloro-5-ciano-2-metilnicotinato (0.084 g, 0.354 mmol), clorhidrato de N-(bencilsulfonil)piperidin-4-carboxamida (0.100 g, 0.354 mmol, véase Ejemplo 34(d)), y DIPEA (0.185 mL, 1.06 mmol), se suspendieron en EtOH (3 mL) y luego se hicieron refluir durante 1 hora. La mezcla de reacción se enfrió a temperatura de la sala y se concentró bajo presión reducida. Se agregó EtOAc (50 mL) y la mezcla de reacción se lavó con NH_4Cl saturado (2 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo ciclopropil 6-(4-(bencilsulfonilcarbamoil)piperidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.098 g (57.2%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.83 (4H, m), 1.59-1.71 (2H, m), 1.79-1.88 (2H, m), 2.54-2.61 (1H, m), 2.64 (3H, s), 3.08-3.20 (2H, m), 4.21-4.30 (1H, m), 4.49-4.59 (2H, m), 4.70 (2H, s), 7.26-7.33 (2H, m), 7.73-7.44 (3H, m), 8.31 (1H, s), 11.6 (1H, s). MS $^m/_z$: 483 (M+1).

Ejemplo 59

Ciclobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico (0.080 g, 0.181 mmol) y mallas moleculares (4Å, 0.100 g) se disolvieron en ciclo-butanol (1 mL) y DMSO (2 mL) y se agitaron a temperatura de la sala durante 1 hora. Se agregó hidruro de sodio (95%, 0.014 g, 0.542 mmol) a la mezcla de reacción y se agitó durante 2 horas a temperatura de la sala. Se agregó EtOAc (30 mL) y la mezcla de reacción se filtró a través de celita. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. La mezcla de reacción se concentró bajo presión reducida. Se agregó agua (30 mL) y el acuoso se lavó con EtOAc (3 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (20% EtOAc en hexanos con 0.1% AcOH) y

trituración (1 / 1 - Et_2O / hexanos) produjo ciclobutil 6-(3-{[(bencilsulfonil) amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.020 g (23%).

^1H NMR (400 MHz, DMSO-d_6): δ 1.61-1.71 (1H, m), 1.77-1.85 (1H, m), 2.10-2.22 (2H, m), 2.29-2.40 (2H, m), 2.64 (3H, s), 3.53-3.60 (1H, m), 4.27-4.35 (2H, m), 4.38-4.46 (2H, m), 4.75 (2H, s), 5.04-5.13 (1H, m), 7.31-7.43 (5H, m), 8.35 (1H, s), 11.8 (1H, s). MS $^m/_z$: 469 (M+1).

Ejemplo 60

2-Hidroxietil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico y mallas moleculares (4Å, 0.100 g) se disolvieron en etilén glicol (2 mL) y DMSO (2 mL) y se agitaron a temperatura de la sala durante 1 hora. Se agregó hidruro de sodio (95%, 0.017 g, 0.678 mmol) a la mezcla de reacción y se agitó durante 2 horas a temperatura de la sala. Se agregó EtOAc (50 mL) y la mezcla de reacción se filtró a través de celita. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. La mezcla de reacción se concentró bajo presión reducida. Se agregó agua (30 mL) y el acuoso se lavó con EtOAc (3 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. El calentamiento (50% EtOAc en hexanos a 50 °C) produjo 2-hidroxietil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.038 g (37.1%).

^1H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.54-3.60 (1H, m), 3.65-3.71 (2H, m), 4.16-4.23 (2H, m), 4.28-4.33 (2H, m), 4.39-4.48 (2H, m), 4.76 (2H, s), 4.91-4.99 (1H, m), 7.31- 7.43 (5H, m), 8.46 (1H, s), 11.8 (1H, s). MS $^m/_z$: 459 (M+1).

Ejemplo 61

Bencil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico (0.100 g, 0.226 mmol) y mallas moleculares (4Å, 0.100 g) se disolvieron en alcohol bencílico (5 mL) y DMSO (1 mL) y se agitaron a temperatura de la sala durante 1 hora. Se agregó hidruro de sodio (95%, 0.017 g, 0.678 mmol) a la mezcla de reacción y se agitó durante 60 horas a temperatura de la sala. Se agregó EtOAc (50 mL) y la mezcla de reacción se filtró a través de celita. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. La mezcla de reacción se concentró bajo presión reducida. Se agregó agua (30 mL) y el acuoso se lavó con EtOAc (3 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (hexanos, luego 20% EtOAc en hexanos, y 20% EtOAc en hexanos con 0.1% AcOH) produjo bencil 6-(3-{[(bencilsulfonil) amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.013 g (12%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.65 (3H, s), 3.51-3.59 (1H, m), 4.27-4.47 (4H, m), 4.75 (2H, s), 5.28 (2H, s), 7.29-7.52 (10H, m), 8.35 (1H, s), 11.8 (1H, s).

Ejemplo 62

Isopropil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino} carbonil) piperidin-1-il]-2-metilnicotinato

(a) 1-(3,4-Diclorofenil)metanosulfonamida

Cloruro de 1-(3,4-diclorofenil)metanosulfonilo (1.00 g, 3.85 mmol) y amoníaco (1.0 M en THF, 38.5 mL, 38.5 mmol) se suspendieron en THF (2 mL) y se agitaron a temperatura de la sala durante 2 horas. La mezcla de reacción se concentró bajo presión reducida. Se agregó EtOAc (50 mL) y los orgánicos se lavaron con $NaHCO_3$ saturado (2 x 30 mL), se secaron

($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo, el cual se utilizó sin purificación adicional. Rendimiento: 0.900 g (97.3%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.31 (2H, s), 6.90 (2H, s), 7.33-7.40 (1H, m), 7.59-7.70 (2H, m).

(b) Isopropil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Ácido 1-(3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico (0.200 g, 0.604 mmol), EDCI (0.174 g, 0.905 mmol), HOBt (0.090 g, 0.664 mmol), (3,4-diclorofenil)metanosulfonamida (0.174 g, 0.724 mmol) y DIPEA (0.315 mL, 1.81 mmol) se suspendieron en DCM (10 mL) a temperatura de la sala y se agitaron durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo isopropil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato como un sólido. Rendimiento: 0.292 g (87%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.56-1.70 (2H, m), 1.78-1.89 (2H, m), 2.54-2.62 (1H, m), 2.65 (3H, s), 3.08-3.20 (2H, m), 4.46-4.59 (2H, m), 4.77 (2H, s), 5.02-5.14 (1H, m), 7.25-7.32 (1H, m), 7.54 (1H, s), 7.67-7.76 (1H, m), 8.33 (1H, s), 11.7 (1H, s). MS $^m/_z$: 553 (M+1).

Ejemplo 63

Etil 5-ciano-6-[3-({[(3,4-diclorobencil)sulfonil]amino}carbonil} azetidin-1-il]-2-metilnicotinato

Ácido 1-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il)azetidin-3-carboxílico (0.200 g, 0.691 mmol), EDCI (0.199 g, 1.04 mmol), HOBt (0.103 g, 0.760 mmol), 1-(3,4-diclorofenil)metanosulfonamida (0.199 g, 0.830 mmol) y DIPEA (0.361 mL, 2.07 mmol) se suspendieron en DCM

(10 mL) a temperatura de la sala y se agitaron durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo etil 5-ciano-6-[3-({[(3,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato como un sólido. Rendimiento: 0.248 g (70%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.53-3.64 (1H, m), 4.19-4.35 (4H, m), 4.38-4.48 (2H, m), 4.82 (2H, s), 7.31-7.39 (1H, m), 7.59-7.70 (2H, s), 8.31 (1H, s), 11.9 (1H, s). MS $^m/_z$: 511 (M+1).

Ejemplo 64

Etil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Ácido 1-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico (0.200 g, 0.630 mmol), EDCI (0.181 g, 0.945 mmol), HOBt (0.094 g, 0.693 mmol), (3,4-diclorofenil)metanosulfonamida (0.182 g, 0.756 mmol) y DIPEA (0.329 mL, 1.89 mmol) se suspendieron en DCM (10 mL) a temperatura de la sala y se agitaron durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo etil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato como un sólido. Rendimiento: 0.273 g (80.3%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.1 Hz), 1.57-1.70 (2H, m), 1.80-1.88 (2H, m), 2.65 (3H, s), 3.10-3.18 (2H, m), 4.31 (1H, s), 4.25 (2H, q, J = 7.1 Hz), 4.50-4.58 (2H, m), 4.76 (2H, s), 7.25-7.32 (1H, m),

7.54 (1H, s), 7.68-7.75 (1H, m), 8.35 (1H, s), 11.7 (1H, s). MS $^{m}/_{z}$: 539 (M+1).

Ejemplo 65

Isopropil 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

(a) (4-Cianofenil)metanosulfonato de sodio

4-(Clorometil)benzonitrilo (5.00 g, 33.0 mmol) y sulfito de sodio (4.42 g, 42.9 mmol) se suspendieron en una solución al 30% de acetona en agua (100 mL) y se agitaron a reflujo durante 4 horas. La solución se concentró bajo presión reducida. Se agregó 95% EtOH (300 mL) y la solución se calentó a 50 °C. A continuación, la solución se enfrió a 0 °C y se filtró para proporcionar el producto crudo como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 7.43 g (103%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.80 (2H, s), 7.45-7.53 (2H, m), 7.68-7.76 (2H, m).

(b) Cloruro de (4-cianofenil)metanosulfonilo

(4-Cianofenil)metanosulfonato de sodio (7.43 g, 33.9 mmol) se suspendió en DCM (250 mL) y se agitó a 0 °C. Se agregó pentacloruro de fósforo (17.7 g, 84.7 mmol) y luego la solución se calentó y se agitó a temperatura de la sala durante 16 horas. Se agregó agua (100 mL) y se agitó durante 5 minutos. Las capas se separaron y los orgánicos se lavaron con salmuera (2 x 100 mL), se secaron ($MgSO_4$), se filtraron y se concentraron a un aceite, el cual se solidificó al reposar y se empleó sin purificación adicional. Rendimiento: 7.00 g (96%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.86 (2H, s), 7.43-7.54 (2H, m), 7.70-7.79 (2H, m).

(c) 1-(4-Cianofenil)metanosulfonamida

Cloruro de 1-(4-cianofenil)metanosulfonilo (1.00 g, 4.64 mmol) se suspendió en DCM (25 mL) y se agitó a temperatura de la sala. Se agregó

hidróxido de amonio (6.00 mL, 46.4 mmol) y la solución se agitó a temperatura de la sala durante 3 horas. Las capas se separaron y el acuoso se lavó con DCM (2 x 40 mL). Los orgánicos combinados se secaron ($MgSO_4$), se filtraron y se concentraron a un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 0.888 g (98%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (2H, s), 6.94 (2H, s), 7.51-7.61 (2H, m), 7.82-7.92 (2H, m).

(d) Isopropil 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Ácido 1-(3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico (0.200 g, 0.604 mmol), EDCI (0.174 g, 0.905 mmol), HOBt (0.090 g, 0.664 mmol), (4-cianofenil)metanosulfonamida (0.118 g, 0.604 mmol) y DIPEA (0.315 mL, 1.81 mmol) se suspendieron en DCM (10 mL) a temperatura de la sala y se agitaron durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo isopropil 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato como un sólido. Rendimiento: 0.232 g (75%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.56-1.70 (2H, m), 1.80-1.89 (2H, m), 2.54-2.63 (1H, m), 2.65 (3H, s), 3.08-3.19 (2H, m), 4.49-4.58 (2H, m), 4.84 (2H, s), 5.03-5.13 (1H, m), 7.47-7.54 (2H, m), 7.88-7.94 (2H, m), 8.33 (1H, s), 11.7 (1H, s). MS $^m/_z$: 510 (M+1).

Ejemplo 66

Etil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato

Ácido 1-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il)azetidin-3-carboxílico (0.200 g, 0.691 mmol), EDCI (0.199 g, 1.04 mmol), HOBt (0.103 g, 0.760 mmol), (4-cianofenil)metanosulfonamida (0.136 g, 0.691 mmol) y DIPEA (0.361 mL, 2.07 mmol) se suspendieron en DCM (10 mL) a temperatura de la sala y se agitaron durante 16 horas. La mezcla de reacción se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con NH_4Cl saturado (2 x 40 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (20% EtOAc en hexanos, luego 20% EtOAc en hexanos con 0.1% AcOH) produjo etil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato como un sólido. Rendimiento: 0.235 g (73%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.51-3.64 (1H, m), 4.18-4.35 (4H, m), 4.38-4.49 (2H, m), 4.90 (2H, s), 7.53-7.61 (2H, m), 7.82-7.90 (2H, m), 8.32 (1H, s), 11.9 (1H, s). MS $^m/_z$: 468 (M+1).

Ejemplo 67

Isopropil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

(a) 1-(4-Fluorofenil)metanosulfonamida

Gas amoníaco se hizo burbujear a través de THF (50 mL) a 0 °C durante 5 minutos. Se agregó cloruro de 1-(4-fluorofenil)metanosulfonilo (1.00 g, 4.80 mmol) a la mezcla de reacción y el sistema se dejó calentar a temperatura de la sala. Gas amoníaco se hizo burbujear a través del sistema durante 5 minutos más y la mezcla de reacción se dejó agitar durante 30 minutos más. La mezcla de reacción se diluyó con EtOAc (100 mL) y se lavó con NH_4Cl saturado (2 x 50 mL), salmuera, se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar 1-(4-fluorofenil)metanosulfonamida como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 0.91 g (100%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.26 (2H, s), 6.82 (2H, s), 7.18-7.24 (2H, m), 7.38-7.42 (2H, m).

(b) Isopropil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Ácido 1-(3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico (0.190 g, 0.573 mmol), 1-(4-fluorofenil) metanosulfonamida (0.141 g, 0.745 mmol), HOBt (0.101 g, 0.745 mmol) y EDCI (0.143 g, 0.745 mmol) se suspendieron en DCM (4 mL), y se agregó DIPEA (0.300 ml, 1.72 mmol). La mezcla de reacción se agitó de un día para otro a temperatura de la sala y luego se concentró bajo presión reducida. La mezcla cruda de reacción se disolvió en MeOH (1.5 mL) y se agregó gota a gota a una solución rápidamente agitada de $KHSO_4$ (0.380 g, 2.865 mmol) en agua (20 mL). El producto se recogió por filtración, se lavó con agua (3 x 10 mL) y se secó bajo vacío. El producto seco se suspendió en IPA (4 mL) y se agitó y se calentó a 50 °C durante 1 hora. El compuesto se aisló por filtración y se secó bajo alto vacío para producir isopropil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato como un sólido. Rendimiento: 0.150 g (54%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.57-1.70 (2H, m), 1.80-1.89 (2H, m), 2.50-2.65 (1H, m), 2.65 (3H, s), 3.09-3.20 (2H, m), 4.49-4.58 (2H, m), 4.70 (2H, s), 5.04-5.12 (1H, m), 7.21-7.29 (2H, m), 7.30-7.38 (2H, m), 8.32 (1H, s), 11.62 (1H, s). MS $^m/_z$: 503 (M+1).

Ejemplo 68

Isopropil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato

(a) 1-(4-Clorofenil)metanosulfonamida

Gas amoníaco se hizo burbujear a través de THF (50 mL) a 0 °C durante 5 minutos. Se agregó cloruro de 1-(4-fluorofenil)metanosulfonilo (1.00 g, 4.80 mmol) a la mezcla de reacción y el sistema se dejó calentar a temperatura de la sala. Gas amoníaco se hizo burbujear a través del sistema

durante 5 minutos más, y la mezcla de reacción se dejó agitar durante 30 minutos más. La mezcla de reacción se diluyó con EtOAc (100 mL) y se lavó con NH_4Cl (2 x 50 mL) saturada, salmuera, se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar 1-(4-clorofenil)metanosulfonamida como un sólido, el cual se utilizó sin purificación adicional. Rendimiento: 0.91 g (100%).

(b) Isopropil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil) piperidin-1-il]-5-ciano-2-metilnicotinato

Ácido 1-(3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico (0.178 g, 0.537 mmol), (4-clorofenil)metanosulfonamida (0.144 g, 0.698 mmol), HOBt (0.0944 g, 0.698 mmol) y EDCI (0.134 g, 0.698 mmol) se suspendieron en DCM (4 mL), y se agregó DIPEA (0.476 mL, 2.69 mmol). La mezcla de reacción se agitó de un día para otro a temperatura de la sala y luego se concentró bajo presión reducida. La mezcla cruda de reacción se disolvió en MeOH (1.5 mL) y se agregó gota a gota a una solución agitada rápidamente de $KHSO_4$ (0.380 g, 2.865 mmol) en agua (20 mL). El producto se recogió por filtración, se lavó con agua (3 x 10 mL) y se secó bajo vacío. El producto crudo se suspendió en EPA (5 mL) y se agitó y se calentó a 50 °C durante 1 hora. El compuesto se aisló por filtración y se secó bajo alto vacío para producir isopropil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.150 g (52%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (6H, d, J = 6.2 Hz), 1.60-1.70 (2H, m), 1.80-1.89 (2H, m), 2.50-2.65 (1H, m), 2.65 (3H, s), 3.09-3.19 (2H, m), 4.50-4.58 (2H, m), 4.72 (2H, s), 5.04-5.12 (1H, m), 7.31 (2H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.4 Hz), 8.32 (1H, s), 11.63 (1H, s). MS $^m/_z$: 519 (M+1).

Ejemplo 69

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-isopropilnicotinato

(a) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-isopropilpiridin-2-il]azetidin-3-carboxílico

A una solución de etil 6-cloro-5-ciano-2-isopropilnicotinato (0.286 g, 1.13 mmol) y DIPEA (0.591 mL, 3.40 mmol) en DMF (3.0 ml) se agregó ácido azetidin-3-carboxílico (0.132 g, 1.31 mmol) y la mezcla heterogénea resultante se calentó a 90 °C durante 3 horas. La mezcla de reacción se diluyó con EtOAc (75 mL), se lavó con NH_4Cl saturado (3x50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se filtró a través de gel de sílice. Concentración, seguida por cromatografía instantánea (1% HOAc, 20% EtOAc, hexanos) produjo ácido 1-(3-ciano-5-(etoxicarbonil)-6-isopropilpiridin-2-il)azetidin-3-carboxílico como un sólido. Rendimiento: 0.118 g (33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (6H, d, J = 6.6 Hz), 1.37 (3H, t, J = 7.5 Hz), 3.60-3.68 (1H, m), 3.95-4.02 (1H, m), 4.31 (2H, q, J = 7.5 Hz), 4.57-4.65 (4H, m), 8.24 (1H, s). MS $^m/_z$: 318 (M+1).

(b) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-isopropilnicotinato

Una solución de ácido 1-(3-ciano-5-(etoxicarbonil)-6-isopropilpiridin-2-il) azetidin-3-carboxílico (0.115 g, 0.362 mmol), EDCI (0.0834 g, 0.435 mmol), HOBtxH_2O (0.0666 g, 0.435 mmol), 1-fenilmetanosulfonamida (0.0620 g, 0.362 mmol) y DIPEA (0.189 mL, 1.09 mmol) en DCM (3.0 mL) se agitó a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó con NH_4Cl saturado (2 x 40 mL) y salmuera (40 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar producto crudo. Cromatografía instantánea (1% MeOH, 1% HOAc, DCM) produjo etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-isopropilnicotinato como un sólido. Rendimiento: 0.125 g (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (6H, d, J = 6.6 Hz), 1.38 (3H, t, J = 6.8), 3.29-3.36 (1H, m), 3.96-4.02 (1H, m), 4.32 (2H, q, J = 6.8 Hz), 4.45-4.46 (4H, m), 4.69 (2H, s), 7.36-7.43 (5H, m), 7.56 (1H, br s), 8.24 (1H, s). MS $^m/_z$: 471 (M+1).

Ejemplo 70

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-etilnicotinato

(a) Ácido 1-(3-ciano-5-(etoxicarbonil)-6-etilpiridin-2-il)azetidin-3-carboxílico

A una solución de etil 6-cloro-5-ciano-2-etilnicotinato (0.290 g, 1.22 mmol) y DIPEA (0.635 mL, 3.65 mmol) en DMF (3.0 mL) se agregó ácido azetidin-3-carboxílico (0.135 g, 134 mmol) y la mezcla heterogénea resultante se calentó a 90 °C durante 3 horas. La mezcla de reacción se diluyó con EtOAc (75 mL), se lavó con NH_4Cl saturado (3x50 mL), salmuera (50. mL), se secó ($MgSO_4$) y se filtró a través de gel de sílice. Concentración, seguida por cromatografía instantánea (1% HOAc, 20% EtOAc, hexanos) produjo ácido 1-(3-ciano-5-(etoxicarbonil)-6-etilpiridin-2-il)azetidin-3-carboxílico como un sólido. Rendimiento: 0.047 g 1%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (3H, t, J = 7.4 Hz), 1.37 (3H, t, J = 7.0 Hz), 3.10 (2H, q, J = 7.4 Hz), 3.60-3.68 (1H, m), 4.31 (2H, q, J = 7.4 Hz), 4.58-4.66 (4H, m), 8.27 (1H, s). MS $^m/_z$: 304 (M+1).

(b) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-etilnicotinato

Una solución de ácido 1-(3-ciano-5-(etoxicarbonil)-6-etilpiridin-2-il)azetidin-3-carboxílico (0.0450 g, 0.148 mmol), EDCI (0.0341 g, 0.178 mmol), HOBt x.H_2O (0.0273 g, 0.178 mmol), 1-fenilmetanosulfonamida (0.0254 g, 0.148 mmol) y DIPEA (0.0775 mL, 0.445 mmol) en DCM (3.0 mL) se agitó a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó con NH_4Cl saturado (2 x

40 mL) y salmuera (40 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar producto crudo. Cromatografía instantánea (1% MeOH, 1% HOAc, DCM) produjo etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-etilnicotinato como un sólido. Rendimiento: 0.055 g (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (3H, t, J = 7.6 Hz), 1.38 (3H, t, J = 7.1 Hz), 3.11 (2H, q, J = 7.6 Hz), 3.29-3.36 (1H, m), 4.32 (2H, q, J = 7.1 Hz), 4.45-4.47 (4H, m), 4.69 (2H, s), 7.36-7.44 (5H, m), 7.57 (1H, br s), 8.28 (1H, s). MS $^m/_z$: 457 (M+1).

Ejemplo 71

Etil 5-ciano-2-metil-6-[3-({[(1-feniletil)sulfonil]amino} carbonil) azetidin-1-il]nicotinato

(a) N-(*terc*-Butil)-1-fenilmetanosulfonamida

A una solución de cloruro de fenilmetanosulfonilo (10.6 g, 55.7 mmol) y *terc*-butilamina (23.6 mL, 223 mmol) en DCM (200 mL) a 0 °C se agregó DIPEA (29.1 mL, 167 mmol). La mezcla de reacción se calentó a temperatura de la sala, se agitó durante 16 horas y luego se concentró. La mezcla se diluyó con EtOAc (1000 mL), se lavó con NH_4Cl saturado (2x250 mL), $NaHCO_3$ saturado (2x250 mL), salmuera (50 mL), se secó ($MgSO_4$) y se filtró a través de gel de sílice. El sólido crudo se sonicó en una mezcla de Et_2O (100 mL) y hexanos (50 mL) para producir cristales, los cuales se recogieron y se lavaron con 1:1 EtOAC/hexanos (50 mL) y hexanos puros (50 mL). Rendimiento: 5.32 g (44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (9H, s), 3.93 (1H, br s), 4.24 (2H, s), 7.35-7.41 (5H, m).

(b) N-(*terc*-Butil)-1-feniletanosulfonamida

A una solución de N-(*terc*-butil)-1-fenilmetanosulfonamida (0.918 g, 4.04 mmol) en THF (40 mL) enfriada a -78 °C se agregó gota a gota *terc*-butil litio (1.70 M en pentano, 4.75 mL, 8.08 mmol). La reacción se calentó a 0

°C durante 1 hora y luego se enfrió a -78 °C. La adición gota a gota de yodometano (0.252 mL, 4.04 mmol) produjo una mezcla turbia, la cual se agitó a -78 °C durante 15 minutos, luego a 0°C durante 1 hora. La mezcla de reacción se extinguió con NH_4Cl saturado (25 mL), se diluyó con EtOAc (75 mL), se lavó con NH_4Cl saturado (3x50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se filtró a través de gel de sílice. Concentración seguida por cromatografía instantánea (DCM) produjo N-(*terc*-butil)-1-feniletanosulfonamida como un aceite. Rendimiento: 0.900 g (92%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (9H, s), 1.78 (3H, d, J = 7.3 Hz), 3.69 (1H, br s), 4.18 (1H, q, J = 7.3 Hz), 7.33-7.39 (3H, m), 7.42-7.45 (2H, m).

(c) 1-Feniletanosulfonamida

Una solución de N-(*terc*-butil)-1-feniletanosulfonamida (0.900 g, 3.73 mmol) se agitó en TFA (50 mL) durante 24 horas. Concentración seguida por destilación a temperatura fija de tolueno (2 x 50 mL) produjo el producto crudo, el cual se disolvió en DCM (25 mL) y se pasó a través de gel de sílice produciendo 1-feniletanosulfonamida como un sólido. Rendimiento: 0.210 g (30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (3H, d, J = 7.2 Hz), 4.27-4.33 (3H, m), 7.38-7.42 (3H, m), 7.45-7.48 (2H, m).

(d) Etil 5-ciano-2-metil-6-[3-({[(1-feniletil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato

Una solución de ácido 1-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il)azetidin-3-carboxílico (0.0700 g, 0.242 mmol), EDCI (0.0649 g, 0.339 mmol), HOBtXH_2O (0.0519 g, 0.339 mmol), 1-feniletanosulfonamida (0.0628 g, 0.0.339 mmol) y DIPEA (0.126 mL, 0.726 mmol) en DCM (3.0 mL) se agitó a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con EtOAc (50 mL) y se lavó con NH_4Cl saturado (2 x 40 mL) y salmuera (40 mL). Los orgánicos se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar producto crudo. Cromatografía instantánea (1% MeOH, 1% HOAc, DCM) produjo etil 5-

ciano-2-metil-6-[3-({[(1-feniletil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato como un sólido. Rendimiento: 0.105 g (95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.0 Hz), 1.88 (3H, d, J = 7.2 Hz), 2.72 (3H, s), 3.17-3.24 (1H, m), 4.25-4.48 (6H, m), 4.86 (1H, q, J = 7.2 Hz), 7.40-7.44 (5H, m), 8.28 (1H, s). MS $^m/_z$: 457 (M+1).

Ejemplo 72

Propil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico (0.080 g, 0.181 mmol) y mallas moleculares (4Å, 0.100 g) se disolvieron en n-propanol (2 mL) y DMSO (2 mL) y se agitaron a temperatura de la sala durante 1 hora. Se agregó hidruro de sodio (95%, 0.014 g, 0.542 mmol) a la mezcla de reacción y se agitó de un día para otro a temperatura de la sala. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. El sólido se filtró y se recogió. La mezcla de reacción se concentró bajo presión reducida. Se agregó agua (30 mL) y el acuoso se lavó con EtOAc (3 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido, el cual se combinó con el sólido filtrado. Cromatografía instantánea (10% EtOAc en hexanos con 0.1% AcOH) produjo propil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.020 g (24.2%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (3H, t, J = 7.4 Hz), 1.74-1.82 (2H, m), 2.73 (3H, s), 3.29- 3.36 (1H, m), 4.22 (2H, t, J = 6.7 Hz), 4.44-4.50 (4H, m), 4.69 (2H, s), 7.35-7.45 (5H, m) 8.29 (1H, s). MS $^m/_z$: 457 (M+1).

Ejemplo 73

Isobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato

Etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico (0.080 g, 0.181 mmol) y mallas moleculares (4Å,

0.100 g) se disolvieron en iso-butanol (2 mL) y DMSO (2 mL) y se agitaron a temperatura de la sala durante 1 hora. Se agregó hidruro de sodio (95%, 0.014 g, 0.542 mmol) a la mezcla de reacción y se agitó durante 4 horas a temperatura de la sala. Se agregó EtOAc (30 mL) y la mezcla de reacción se filtró a través de celita. Se agregó HCl (concentrado) gota a gota a la mezcla hasta que el pH se redujo a pH 2. La mezcla de reacción se concentró bajo presión reducida. Se agregó agua (30 mL) y el acuoso se lavó con EtOAc (3 x 50 mL), se secó ($MgSO_4$) y se concentró bajo presión reducida para proporcionar el producto crudo como un sólido. Cromatografía instantánea (10% EtOAc en hexanos con 0.1% AcOH) produjo isobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.040 g (47.0%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (6H, d, J = 6.7 Hz), 2.02-2.10 (1H, m), 2.73 (3H, s), 3.30-3.37 (1H, m), 4.05 (2H, d, J = 6.6 Hz), 4.42-4.50 (4H, m), 4.69 (2H, s), 7.36-7.44 (5H, m), 8.28 (1H, s). MS $^m/_z$: 471 (M+1).

Ejemplo 74

Isopropil 5-ciano-2-metil-6-{4-[({[4-(trifluorometil)bencil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato

(a) 1-[4-(Trifluorometil)fenil]metanosulfonamida

Cloruro de 1-(4-(trifluorometil)fenil)metanosulfonilo (1.00 g, 3.87 mmol) y amoníaco (1.0 M en THF, 38.7 mL, 38.7 mmol) se suspendieron en THF (2 mL) y se agitaron a temperatura de la sala durante 16 horas. La mezcla de reacción se concentró bajo presión reducida. Se agregó EtOAc (50 mL) y los orgánicos se lavaron con $NaHCO_3$ saturado (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar 1-(4-(trifluorometil)fenil)metanosulfonamida, la cual se utilizó sin purificación adicional. Rendimiento: 0.900 g (97.3%).
^{1}H NMR (400 MHz, DMSO-d_6): δ 4.40 (2H, s), 6.94 (2H, s), 7.60 (2H, d, J = 8.1 Hz), 7.75 (2H, d, J = 8.1 Hz).

^{1}H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.64 (2H, m), 1.87 (2H, m), 2.61 (1H, m), 2.64 (3H, s), 3.15 (2H, m), 4.53 (2H, m), 4.75 (2H, s), 5.07 (1H, m), 7.24-7.47 (4H, m), 8.31 (1H, s), 11.74 (1H, s). MS $^m/_z$: 503 (M+1).

Ejemplo 79

Isopropil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato

TBTU (0.097 g, 0.302 mmol) y DIPEA (0.074 g, 0.574 mmol) se agregaron a una solución de ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.100 g, 0.302 mmol) en DCM (2 mL) y la mezcla se agitó a temperatura de la sala durante 2.5 horas. La mezcla se agregó a 1-(3-clorofenil)metanosulfonamida (0.074 g, 0.360 mmol) en DCM (2 mL) y la agitación se continuó durante 18 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM (3 veces). La fase orgánica combinada se filtró a través de un separador de fase y se evaporó para proporcionar un producto crudo. Purificación mediante HPLC preparativa (Kromasil C8, columna 21.5 x 100 mm, caudal 25 mL/minuto empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) proporcionó el producto puro como un sólido. Rendimiento: 0.118 g (75%).

^{1}H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.62 (2H, m), 1.82 (2H, m), 2.58 (1H, m), 2.63 (3H, s), 3.13 (2H, m), 4.52 (2H, m), 4.74 (2H, s), 5.07 (1H, m), 7.24-7.47 (4H, m), 8.31 (1H, s), 11.66 (1H, s). MS $^m/_z$: 520 (M+1).

Ejemplo 80

Isopropil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato

TBTU (0.097 g, 0.302 mmol) y DIPEA (0.074 g, 0.574 mmol) se agregaron a una solución de ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.100 g, 0.302 mmol) en DCM (2 mL) y la mezcla se agitó a temperatura de la sala durante 2.5 horas. La mezcla se

agregó a 1-(2-clorofenil)metanosulfonamida (0.074 g, 0.360 mmol) en DCM (2 mL) y la agitación se continuó durante 18 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM (3 veces). La fase orgánica combinada se filtró a través de un separador de fase y se evaporó para proporcionar un producto crudo. Purificación mediante HPLC preparativa (Kromasil C8, columna 21.5 x 100 mm, caudal 25 mL/minuto empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) proporcionó el producto puro como un sólido. Rendimiento: 0.116 g (74%).
^1H NMR (500 MHz, DMSO-d_6): 1-29 (6H, d), 1.65 (2H, m), 1.89 (2H, m), 2.63 (1H, m), 2.63 (3H, s), 3.15 (2H, m), 4.53 (2H, m), 4.85 (2H, s), 5.07 (1H, m), 7.38-7.54 (4H, m), 8.31 (1H, s), 11.80 (1H, s). MS $^m/_z$: 520 (M+1).

Ejemplo 81

Etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato

y ({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il} carbonil) [(4-metilbencil)sulfonil]azanida de sodio

TBTU (1.162 g, 3.62 mmol) y DIPEA (2.04 g, 15.76 mmol) se agregaron a una solución de ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il] piperidin-4-carboxílico (0.100 g, 0.302 mmol) en DCM (53 mL) y la mezcla se agitó a temperatura de la sala durante 5 minutos. Se agregó 1-(4-metilfenil)metanosulfonamida (0.67 g, 3.62 mmol) y la agitación se continuó de un día para otro. La mezcla de reacción se concentró y se repartió en porciones entre EtOAc (200 mL), agua (50 mL) y ácido fórmico (5 mL). La fase orgánica se separó y se evaporó para producir un sólido color rosado, crudo, el cual se purificó mediante HPLC preparativa (Kromasil C8, con una gradiente de 0.1 M NH_4OAc y CH_3CN) para producir etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato como un sólido blancuzco. Rendimiento: 0.687 g (45%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 11 Hz), 1.56 - 1.68 (2H, m), 1.79 - 1.87 (2H, m), 2.29 (3H, s), 2.41-2.60 (1H, m, concealed under the DMSO-peak), 2.64 (3H, s), 3.09 - 3.18 (2H, m), 3.29 (1H, s), 4.24 (2H, q, J = 7.1 Hz), 4.48 - 4.56 (2H, m), 4.59 (2H, s), 7.13 - 7.21 (4H, m), 8.33 (1H, s). MS $^m/_z$: 485 (M+1).

Etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato (0.687 g, 1.38 mmol) se disolvió en CH_3CN/agua y se agregó 1M NaOH (1.38 mL) y la mezcla se secó por congelamiento para producir ({1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-il} carbonil)[(4-metilbencil)sulfonil]azanida de como un sólido blanco. Rendimiento: 0.726 g (104%, que contenía algo de agua residual).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.51 - 1.65 (2H, m), 1.74 - 1.82 (2H, m), 2.17 - 2.23 (1H, m), 2.25 (3H, s), 2.63 (3H, s), 3.14 - 3.25 (2H, m), 4.17 (2H, s), 4.24 (2H, q, J = 7.1 Hz)$_5$ 4.37 - 4.45 (2H, m), 7.03 (2H, d, J = 8.1 Hz), 7.10 (2H, d, J = 8.1 Hz), 8.30 (1H, s)

Ejemplo 82

Etil 5-ciano-6-{4-[({[2-(metoxicarbonil)bencil]sulfonil}amino)carbonil] piperidin-1-il}-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 2-[(aminosulfonil) metil]benzoato. Rendimiento = 77 mg (69%).

^{1}H NMR (400 MHz, DMSO-d_6) δ?1.30 (3H, t, J = 7.1 Hz), 1.56 - 1.71 (2H, m), 1.81 - 1.89 (2H, m), 2.48 - 2.53 (1H, m), 2.65 (3H, s), 3.08 - 3.20 (2H, m), 3.83 (3H, s), 4.25 (2H, q, J = 7.1 Hz), 4.46 - 4.61 (2H, m), 5.14 (2H, s), 7.35 (1H, d, J = 7.5 Hz), 7.46 - 7.68 (2H, m), 7.85 (1H, d, J = 7.9 Hz), 8.34 (1H, s), 11.58 - 11.66 (1H, m). MS $^m/_z$: 529 (M+1).

Ejemplo 83

Etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]lamino}carbonil)piperidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-(3-fluorofenil) metanosulfonamida. Rendimiento = 76 mg (74%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.69 (2H, m), 1.78 - 1.87 (2H, m), 2.41-2.60 (1H, m, oculto bajo un pico de DMSO), 2.65 (3H, s), 3.10 - 3.20 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.52 (2H, d, J = 13.3 Hz), 4.72 (2H, s), 7.08 - 7.16 (2H, m), 7.19 - 7.29 (1H, m), 7.45 (1H, q, J = 7.4 Hz), 8.34 (1H, s), 11.67 (1H, s). MS $^m/_z$: 489 (M+1).

Ejemplo 84

Isopropil 5-ciano-2-metil-6-[4-({[2-(2-metilfenil)etil]sulfonil}carbamoil) piperidin-1-il]nicotinato

TBTU (0.097 g, 0.302 mmol) y DIPEA (0.074 g, 0.574 mmol) se agregaron a una solución de ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.100 g, 0.302 mmol) en DCM (2 mL) y la mezcla se agitó a temperatura de la sala durante 2.5 horas. La mezcla se agregó a 2-(2-metilfenil)etanosulfonamida (0.074 g, 0.360 mmol) en DCM (2 mL) y la agitación se continuó durante 18 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM (3 veces). La fase orgánica combinada se filtró a través de un separador de fase y se evaporó para proporcionar un producto crudo. Purificación mediante HPLC preparativa (Kromasil C8, columna 21.5 x 100 mm, caudal 25 mL/minuto empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) proporcionó el producto puro como un sólido. Rendimiento: 0.098 g (63%).

^{1}H NMR (500 MHz, DMSO-d_6): 1.29 (6H, d), 1.59 (2H, m), 1.89 (2H, m), 2.24 (3H, s), 2.63 (1H, m), 2.63 (3H, s), 2.95 (2H, m), 3.15 (2H, m), 3.59 (2H, m), 4.52 (2H, m), 5.07 (1H, m), 7.11-7.18 (4H, m), 8.30 (1H, s), 11.80 (1H, s). MS $^m/_z$: 513 (M+1), 511 (M-1).

Ejemplo 85

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato

(a) Etil 5-acetil-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

Etil 5-acetil-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato se preparó de 3-oxobutanamida empleando la misma metodología que produjo etil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3- carboxilato.

(b) Etil 5-hidroxi-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

A una solución de H_2O_2 (30% en agua, 74.8 mL, 792 mmol) en EtOH (500 mL) enfriada a 0°C se agregó gota a gota TFA (89.5 mL, 1.16 mol). Una suspensión de etil 5-acetil-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (11.8 g, 52.8 mmol) en EtOH (500 mL) se agregó lentamente a la mezcla de reacción, la cual se calentó entonces a reflujo durante 24 horas y luego se dejó enfriar a temperatura de la sala. En un frasco separado, TFA (89.5 mL, 1.16 mol) se agregó gota a gota a una solución de H_2O_2 (30% en agua, 74.8 mL, 792 mmol) en EtOH (100 mL) enfriado a 0°C y se agitó durante 15 minutos. Esta solución se agregó entonces a la mezcla de reacción, la cual se calentó a reflujo durante 18 horas más. Luego de enfriar a temperatura de la sala, la mezcla se concentró bajo presión reducida se destiló con temperatura fija de tolueno (8 x 100 mL). La adición de CH_3CN (100 mL) produjo un sólido, el cual se recogió y se lavó CH_3CN (100 mL). Rendimiento: 2.50 g (24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 1.37 (3H, t, J = 7.1 Hz), 2.66 (3H, s), 4.31 (2H, q, J = 7.1 Hz), 6.35 (1H, br s), 7.50 (1H, s), 11.75 (1H, br s). MS $^m/_z$: 196 (M-1).

(c) Etil 5-(4-metoxi-4-oxobutoxi)-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

A una solución de etil 5-hidroxi-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (0.824 g, 4.18 mmol) en DMF (25 mL) enfriado a 0°C se agregó LiH (0.0385 g, 4.60 mmol) y la mezcla resultante se agitó durante 1.5 horas. Se agregaron metil 4-bromobutanoato (0.832 g 4.60 mmol) y TBAI (0.005 g, 0.0135 mmol) y la reacción se calentó a 60 °C durante 20 horas. Luego de enfriar a temperatura de la sala la mezcla se diluyó con EtOAc (200 mL), se lavó con NH_4Cl saturado (3 x 100 mL), salmuera, se secó ($MgSO_4$) y se pasó a través de gel de sílice. Cromatografía instantánea (1:1

EtOAc/hexanos) suministró etil 5-(4-metoxi-4-oxobutoxi)-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido. Rendimiento: 0.60g (48%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J = 7.1 Hz), 2.15-2.22 (2H, m), 2.60 (2H, t , J = 7.1 Hz), 2.73 (3H, s), 3.71 (3H, s), 4.13 (2H, t, J = 6.0 Hz), 4.39 (2H, q, J = 7.1 Hz), 7.70 (1H, s). MS $^m/_z$: 298 (M+1).

(d) Etil 6-cloro-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato

Una suspensión de etil 5-(4-metoxi-4-oxobutoxi)-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (0.600 g, 2.02 mmol) en $POCl_3$ (25 mL) se calentó a 60 °C durante 5 hora. Luego de enfriar a temperatura de la sala, la mezcla de reacción se concentró bajo presión reducida, se diluyó con EtOAc (200 mL), se lavó con $NaHCO_3$ saturado (2 x 100 mL), salmuera, se secó ($MgSO_4$) y se pasó a través de gel de sílice. La concentración proporcionó etil 6-cloro-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato. Rendimiento: 0.589 g (92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J = 7.1 Hz), 2.15-2.22 (2H, m), 2.60 (2H, t, J = 7.1 Hz), 2.74 (3H, s), 3.71 (3H, s), 4.13 (2H, t, J = 6.0 Hz), 4.39 (2H, q, J = 7.1 Hz), 7.70 (1H, s). MS ^{m}/z: 316 (M+1).

(e) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato

Una suspensión de etil 6-cloro-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato (0.300 g, 1.23 mmol), clorhidrato de N-(bencilsulfonil)piperidin-4-carboxamida (0.413 g, 1.30 mmol) y DIPEA (0.371 mL, 2.13 mmol) en NMP (2 mL) se agitó a 80°C durante 24 horas. La mezcla de reacción se enfrió a temperatura de la sala y se virtió en EtOAc (60 mL) y NH_4Cl saturado (30 mL). Los orgánicos se lavaron con agua (3 x 50 mL), salmuera (1 x 50 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el material crudo. Cromatografía instantánea (1:4 EtOAc / hexanos con 1% AcOH) suministró etil 6-(4-{[bencilsulfonil) amino]carbonil}piperidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato como un sólido. Rendimiento: 0.060 g (29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, *J* = 7.1 Hz), 1.78-1.84 (4H, m), 2.11-2.17 (2H, m), 2.32-2.40 (1H, m), 2.52 (2H, t, *J* = 7.2 Hz), 2.65 (3H, s), 2.80-2.87 (2H, m), 3.68 (3H, s), 4.01 (2H, t, *J* = 6.2 Hz), 4.29-4.36 (4H, m), 4.68 (2H, s), 7.35-7.40 (5H, m), 7.54 (1H, s). MS $^m/_z$: 562 (M+1).

Ejemplo 86

Ácido 4-{[2-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico

Una solución de etil 6-(4-{[bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato (0.050 g, 0.089 mmol) en THF (4 mL) se enfrió a 0°C y se trató con NaOH (1.00 M, 0.18 mL, 0.18 mmol). La reacción se calentó a temperatura de la sala y se agitó durante 18 horas. Luego de la dilución con EtOAc (100 mL), la mezcla se lavó con NH_4Cl saturada (2 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$), y se concentró. Cromatografía instantánea (50% EtOAc/hexanos con 1% HOAc) suministró ácido 4-(2-(4-(bencilsulfonilcarbamoil)piperidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-iloxi)butanoico como un sólido. Rendimiento: 0.036 g (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, *J* = 7.1 Hz), 1.82-1.86 (4H, m), 2.06-2.13 (2H, m), 2.39-2.45 (1H, m), 2.50 (2H, t, *J* = 6.9 Hz), 2.65 (3H, s), 2.77-2.84 (2H, m), 4.02 (2H, t, *J* = 6.6 Hz), 4.24-4.27 (2H, m), 4.32 (2H, q, *J* = 7.1 Hz), 4.68 (2H, s), 7.36-7.40 (5H, m), 7.59 (1H, s). MS $^m/_z$: 548 (M+1).

Ejemplo 87

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato

(a) Ácido 1-[5-(etoxicarbonil)-3-(4-metoxi-4-oxobutoxi)-6-metilpiridin-2-il]azetidin-3-carboxílico

Ácido azetidin-3-carboxílico (0.380 g, 3.76 mmol) e hidróxido de tetrabutilamonio (2.3 g, 3.55 mmol, como una solución al 40% en agua) se

combinaron en MeOH. El ácido azetidina se disolvió y la solución se concentró luego *in vacuo* y se destiló a temperatura fija con tolueno dos veces. El aceite resultante se bombeó bajo vacío. Se agregó NMP (9 mL) junto con mallas moleculares de 4 Å secas. La solución resultante se utilizó como una solución 0.35 M de azetidin-3-carboxilato de tetrabutilamonio. Etil 6-cloro-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato (0.060 g, 0.19 mmol) se disolvió en una solución NMP de azetidin-3-carboxilato de tetrabutilamonio (2.0 mL, 0.70 mmol). La reacción se agitó a temperatura de la sala. Luego de 2 horas, la reacción se completó y se virtió en EtOAc (75 mL), se lavó con NH_4Cl (2 x 40 mL) y se secó ($MgSO_4$). La solución se concentró *in vacuo* para proporcionar el producto, ácido 1-[5-(etoxicarbonil)-3-(4-metoxi-4-oxobutoxi)-6-metilpiridin-2-il]azetidin-3-carboxílico, el cual se utilizó sin purificación adicional. Rendimiento = 0.070 g (97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.08-2.15 (2H, m), 2.51 (2H, t, J = 7.3 Hz), 2.63 (3H, s), 3.52-3.59 (1H, m), 3.70 (3H, s), 3.96 (2H, t, J = 6.1 Hz), 4.31 (2H, q, J = 7.1 Hz), 4.22-4.44 (4H, m), 7.40 (1H, s). MS $^m/_z$: 379 (M-1).

(b) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato

Ácido 1-(5-(etoxicarbonil)-3-(4-metoxi-4-oxobutoxi)-6-metilpiridin-2-il) azetidin-3-carboxílico (0.070 g, 0.18 mmol), HOBt (0.032 g, 0.24 mmol), 1-fenilmetanosulfonamida (0.044 g, 0.26 mmol) y EDCI (0.046 g, 0.24 mmol) se disolvieron parcialmente en DCM seco (2.5 mL) y luego se agregó DIPEA (0.16 mL, 0.92 mmol). La reacción se dejó agitar de un día para otro a temperatura de la sala. La reacción se concentró luego con vacío y el residuo se disolvió en MeOH (0.5 mL). La solución resultante se agregó lentamente a una solución de $KHSO_4$ (0.125 g, 0.92 mmol) en agua (7 mL). No se formó un precipitado claro, de modo que la mezcla se repartió en porciones entre EtOAc (40 m) y agua (10 mL). La fase orgánica se lavó con NH_4Cl saturado, luego salmuera, y se secó ($MgSO_4$). La solución se

concentró *in vacuo* y se purificó mediante cromatografía de columna (30% EtOAc/hexanos a 50% EtOAc/hexanos, luego se agregó 0.1% HOAc) para proporcionar etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato como un aceite. Rendimiento: 0.032 g (33%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 2.06-2.13 (2H, m), 2.48 (2H, t, J = 7.3 Hz), 2.62 (3H, s), 3.29-3.36 (1H, m), 3.67 (3H, s), 3.96 (2H, t, J = 6.1 Hz), 4.28-4.34 (6H, m), 4.67 (2H, s), 7.37-7.38 (5H, m), 7.41 (1H, s). MS $^m/_z$: 534 (M+1).

Ejemplo 88

Etil 6-(4-{[(anilinosulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

Ácido 1-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il)piperidin-4-carboxílico (0.155 g, 0.488 mmol) se disolvió parcialmente en DCE seco (4 mL). Se agregó CDI (0.103 g, 0.635 mmol) y la mezcla de reacción se calentó a 50 °C durante 3 horas. Se agregó N-fenilsulfamida [*Bioorganic & Medicinal Chemistry Letters* **2003**, 18, 837] (0.101 g, 0.586 mmol), seguida por DBU (0.0875 mL, 0.586 mmol) y la reacción se calentó a 50 °C durante 16 horas más. La reacción se enfrió y se concentró. El residuo se repartió en porciones entre EtOAc (75 mL) y NH_4Cl acuoso (50 mL), y la fase orgánica se lavó posteriormente con NH_4Cl (40 mL) y salmuera (40 mL). La solución se concentró entonces para proporcionar un sólido blanco, el cual se trituró con MeOH para suministrar el producto deseado, etil 6-(4-{[(anilinosulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato, como un sólido blanco. Rendimiento = 0.16 g (70%).

NMR (400 MHz, DMSO-d_6): δ 1.30 (3H, t, J = 7.1 Hz), 1.36-1.46 (2H, m), 1.63-1.65 (2H, m), 2.45-2.50 (1H, obs), 2.62 (3H, s), 3.09 (2H, d, J = 11.6 Hz), 4.24 (2H, q, J = 7.1 Hz), 4.36-4.39 (2H, m), 7.10 (1H, t, J = 7.4 Hz), 7.15 (2H, d, J = 7.7 Hz), 7.31 (2H, t, J = 7.9 Hz), 8.31 (1H, s), 10.38 (1H, s), 11.73 (1H, s). MS $^m/_z$: 472 (M+1).

Ejemplo 89

Etil 5-ciano-2-metil-6-{4-[({[metil(fenil)amino]sulfonil}amino)carbonil] piperidin-1-il}nicotinato

Etil 5-ciano-2-metil-6-(4-(N-fenilsulfamoilcarbamoil)piperidin-1-il) nicotinato (0.047 g, 0.10 mmol) se disolvió en DMF seco (1 mL) y se enfrió a 0 °C. Se agregó hidruro de sodio (0.010 g, 60% p/p, 0.25 mmol) y la reacción se calentó a temperatura de la sala y luego a 35 °C durante 5 minutos. La reacción se devolvió a 0 °C y luego se agregó yodometano (6.0 µL, 0.010 mmol). Después de 30 minutos, la reacción se calentó a temperatura ambiente y se agitó durante 2 horas. La reacción se acidificó entonces con HOAc (0.2 mL) y se repartió en porciones entre EtOAc (75 mL) y NH_4Cl acuoso (50 mL). La fase orgánica se lavó con NH_4Cl (30 mL), agua (30 mL), se secó ($MgSO_4$) y se concentró *in vacuo*. El producto crudo se purificó mediante cromatografía de columna (30 a 40% EtOAc/hexanos) para suministrar el producto deseado, etil 5-ciano-2-metil-6-(4-(N-metil-N-fenilsulfamoilcarbamoil)piperidin-1-il)nicotinato.

Rendimiento: 0.012 g (25%). Espectroscopia NMR usando NOE confirmó el regioisómero deseado.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 1.71-1.86 (4H, m), 2.35-2.42 (1H, m), 2.72 (3H, s), 3.09-3.16 (2H, m), 3.52 (3H, s), 4.32 (2H, q, J = 7.1 Hz), 4.63-4.67 (2H, m), 7.31-7.41 (5H, m), 8.35 (1H, s). MS $^m/_z$: 486 (M+1).

Ejemplo 90

Isopropil 5-ciano-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato

Preparado de acuerdo con el método C a partir de 1-(4-metilfenil) metanosulfonamida. Rendimiento = 4 mg (4%). MS $^m/_z$: 471 (M+1).

Ejemplo 91

Isopropil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método C a partir de 1-(3-fluorofenil) metanosulfonamida. Rendimiento = 6.4 mg (4.5%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 3.51-3.61 (m, 1H), 4.26-4.34 (m, 2H), 4.38-4.47 (m, 2H), 4.75-4.81 (br s, 2H), 5.04-5.12 (m, 1H), 7.16-7.28 (m, 3H), 7.39-7.48 (m, 1H), 8.30 (s, 1H), 11.88-11.94 (br s, 1H). MS $^m/_z$: 475 (M+1).

Ejemplo 92

Isopropil 5-ciano-2-metil-6-[3-({[(2-feniletil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato

Preparado de acuerdo con el método C a partir de 2-fenilemanesulfonamida. Rendimiento = 31 mg (22%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (d, J = 6.3 Hz, 6H), 2.63 (s, 3H), 3.00-3.07 (m, 2H), 3.52-3.61 (m, 1H), 3.70-3.77 (m, 2H), 4.24-4.32 (m, 2H), 4,38-4.47 (m, 2H), 5.04-5.12 (m, 1H), 7.20-7.35 (m, 5H), 8.29 (s, 1H), 11.88-12.03 (br s, 1H). MS $^m/_z$: 471 (M+1).

Ejemplo 93

Isopropil 5-ciano-6-[3-({[(ciclopentilmetil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método C a partir de 1-ciclopentilmetanosulfonamida. Rendimiento = 28 mg (21%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24- 1.34 (m, 8H), 1.48-1.66 (m, 4H), 1.82-1.92 (m, 2H), 2.17-2.27 (m, 1H), 2.64 (s, 3H), 3.46 (d, J = 6.8 Hz, 2H), 3.57-3.67 (m, 1H), 4.32-4.39 (m, 2H), 4.42-4.51 (m, 2H), 5.04-5.13 (m, 1H), 8.29 (s, 1H), 11.91 (br s, 1H). MS $^m/_z$: 449 (M+1)

Ejemplo 94

Isopropil 5-ciano-6-{3-[({[2-(metoxicarbonil)bencil]sulfonil}amino) carbonil]azetidin-1-il}-2-metilnicotinato

Preparado de acuerdo con el método C a partir de metil 2-[(aminosulfonil) metil]benzoato. Rendimiento = 46 mg (30%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 3.50-3.60 (m, 1H), 3.83 (s, 3H), 4.29-4.36 (m, 2H), 4.38-4.47 (m, 2H), 5.03-5.14 (m, 1H), 5.22 (s, 2H), 7.45-7.48 (m, 1H), 7.52-7.58 (m, 1H), 7.59-7.65 (m, 1H), 7.83-7.87 (m, 1H), 8.31 (s, 1H), 11.83-11.87 (br s, 1H). MS $^m/_z$: (M+1).

Ejemplo 95

Isopropil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método C a partir de 1-(2-fluorofenil) metanosulfonamida. Rendimiento = 53 mg (37%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.66 (s, 3H), 3.57-3.66 (m, 1H), 3.33-4.41 (m, 2H), 4.42-4.52 (m, 2H), 4.83 (s, 2H), 5.03-5.14 (m, 1H), 7.24-7.31 (m, 2H), 7.45-7.53 (m, 2H), 8.31 (s, 1H), 11.99 (br s, 1H). MS $^m/_2$: 515 (M+1).

Ejemplo 96

Isopropil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-metilnicotinato

Preparado de acuerdo con el método C a partir de 1-(4-clorofenil) metanosulfonamida. Rendimiento = 76 mg (52%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.66 (s, 3H), 3.51-3.61 (s, 1H), 4.28-4.36 (m, 2H), 4.38-4.47 (m, 2H), 4.75 (s, 2H), 5.04-5.13 (m, 1H), 7.35-7.40 (m, 2H), 7.43-7.48 (m, 2H), 8.31 (s, 1H), 11.87 (br s, 1H). MS $^m/_z$: 491 (M+1)

Ejemplo 97

Isopropil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método C a partir de 1-(4-fluorofenil) metanosulfonamida. Rendimiento = 19 mg (13%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.32 (d, J = 6.3 Hz, 6H), 2.65 (s, 3H), 3.51-3.61 (m, 1H), 4.27-4.35 (m, 2H), 4.38-4.48 (m, 2H), 4.76 (br s, 2H), 5.04-5.13 (m, 1H), 7.14-7.26 (m, 2H), 7.37-7.48 (m, 2H), 8.31 (s, 1H), 11.81 (br s, 1H). MS $^m/_z$: 475 (M+1).

Ejemplo 98

Isopropil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método C a partir de 1-(4-cianofenil) metanosulfonamida. Rendimiento = 39 mg (27%).

^{1}H NMR (400 MHz, DMSO-d_6/CD_3OD 9:1): δ 1.31 (6H, d, J = 6.3 H), 2.65 (3H s), 3.54-3.63 (1H, m), 4.28-4.35 (2H, m), 4.39-4.48 (2H, m), 4.77 (2H, s), 5.03-5.14 (1H, m), 7.19-7.25 (2H, m), 7.38-7.44 (2H, m), 8.30 (1H, s). MS ^{m}/z: 482 (M+1).

Ejemplo 99

Metil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

(a) Ácido 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxílico

KOH (1.43 g, 25.5 mmol) disuelto en EtOH (25 mL, 95%) se agregó a etil 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (1.69 g, 8.2 mmol) en EtOH(30 mL) para producir una suspensión espesa (***"a thick slurry"***), la cual se calentó a reflujo (90 grados en el baño de aceite) durante 12 horas. La mezcla se concentró y se agregó 2 M HCl. El precipitado formado se filtró, se lavó con agua y se secó para producir ácido 5-ciano-2-metil-6-oxo-

1,6-dihidropiridin-3-carboxílico, como un sólido blanco. Rendimiento: 1.425 g (98%).

^{1}H NMR (500MHz, DMSO-d_6): forma ceto: 2.61 (3H, s), 8.40 (1H, s), 12.91 (1H, br s). ~86% forma enol: 2.36 (3H, s), 8.09 (1H, s), 10.50 (1H, br s). ~14% MS $^m/_z$: 179(M+1), 177(M-1).

(b) Cloruro de 6-cloro-5-ciano-2-metilnicotinoilo

Cloruro de oxalilo (3.38 mL, 40 mmol) se agregó gota a gota a una suspensión fría (baño de hielo/agua) de ácido 5-ciano-2-metil-6-oxo-1,6-dihidropiridin-3-carboxílico (0.710 g, 3.99 mmol) en DCM seco (25 mL), seguido por DMF seco (0.1 mL). La reacción se agitó durante 20 minutos a 0 grados y luego a temperatura de la sala durante 30 minutos, seguida por reflujo durante 16 horas. La mezcla se evaporó y el residuo negro remanente se co-evaporó con DCM seco (dos veces). El producto crudo se utilizó en el siguiente paso sin purificación adicional.

(c) Metil 6-cloro-5-ciano-2-metilnicotinato

DPEA (0.35 mL, 2.0 mmol) se agregó a una solución de cloruro de 6-cloro-5-ciano-2-metilnicotinoilo crudo (0.222 g, 1.03 mmol) en metanol (4 mL). La reacción se agitó a temperatura de la sala durante 1 hora. La mezcla de reacción se utilizó directamente en el siguiente paso sin aislamiento.

(d) Ácido 1-[3-ciano-5-(metoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico

Ácido piperidin-4-carboxílico (0.136 g, 1.05 mmol) se agregó a la solución anterior (asumiendo una conversión del 100%, 0.210 g, 1 mmol) y la mezcla se calentó a 120 grados en un horno microondas de nodo simple durante 5 minutos. Se agregó NH_4C (acuoso) y la reacción se extrajo con DCM (3 veces). La capa orgánica combinada separada se secó y se evaporó. Purificación mediante HPLC preparativa (Kromasil C8, columna 21.5 x 250 mm, caudal 25 mL/minuto, empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) produjo 0.181 g de ácido 1-[3-ciano-5-

(metoxicarbonil)-6-metilpiridin-2-il] piperidin-4-carboxílico. Rendimiento (60% en tres pasos).

^{1}H NMR (500MHz, DMSO-d_6): 1.54-1.63 (2H, m), 1.85-1.92 (2H, m), 2.39-2.47 (1H, m), 2.62 (3H, s), 3.22-3.29 (2H, m), 3.77 (3H, s), 4.38-4.44 (2H, m), 8.30 (1H, s).

(e) Metil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

TBTU (0.106 g, 0.33 mmol) se agregó a una solución de ácido 1-[3-ciano-5-(metoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (0.090 g, 0.297 mmol) y DIPEA (0.2 mL, 1.15 mmol) en DCM (4 mL). Se agregó fenilmetanosulfonamida (0.060 g, 0.409 mmol) después de 30 minutos y la reacción se agitó durante 20 horas a temperatura de la sala. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM (3 veces). La capa orgánica combinada se secó y se evaporó para proporcionar un producto crudo, el cual se purificó mediante HPLC de fase inversa (Kromasil C8, columna 21.5 x 250 mm, caudal 25 mL/minuto, empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) para producir metil 6-(4-{[(bencilsulfonil) amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato como un polvo. Rendimiento: 0.040 g (29%).

^{1}H NMR (500MHz, DMSO-d_6): 1.58-1.68 (2H, m), 1.80-1.87 (2H, m) 2.54-2.61 (1H, m), 2.64 (3H, s), 3.13 (2H, apparent t), 3.78 (3H, s), 4.53 (2H, apparent d), 4.68 (2H, s), 7.26-7.31 (2H, m), 7.36-7.42 (3H, m), 8.32 (1H, s), 11.60 (1H, bs).

Ejemplo 100

Metil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato

Preparado en la misma forma como se describe en Ejemplo 99 reemplazando fenilmetanosulfonamida por 1-(4-metilfenil) metanosulfonamida. Rendimiento: 0.034 g (24%).

^{1}H NMR (500MHz, DMSO-d_6): 1.58-1.63 (2H, m), 1.80-1.87 (2H, m), 2.30 (3H, s), 2.53-2.62 (1H, m), 2.64 (3H, s), 3.13 (2H, aparente), 3.78 (3H s), 4.53 (2H, aparente d), 4.63 (2H, s), 7.14-7.22 (4H, m), 8.33 (1H, s), 11.55 (1H, bs).

Ejemplo 101

S-Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilpiridin-3-carbotioato

(a) S-Etil 6-cloro-5-ciano-2-metilpiridin-3-carbotioato

Una solución de EtSH (0.22 mL, 3.0 mmol) y DIPEA (1 mL, 5.74 mmol) en THF (5 mL se agregó gota a gota a una solución fría (baño de hielo/agua a 0 grados) de cloruro de 6-cloro-5-ciano-2-metilnicotinoilo (0.60 g, 2.29 mmol, véase Ejemplo 99 anterior). La reacción se agitó a 0 grados durante 10 minutos, seguida por temperatura de la sala durante 50 minutos. La mezcla se evaporó y el residuo se co-evaporó con THF (3 veces) para producir S-etil 6-cloro-5-ciano-2-metilpiridin-3-carbotioato, el cual se utilizó en el siguiente paso sin purificación adicional. Rendimiento: 0.671 g (100%).

(b) Ácido 1-{3-ciano-5-[(etiltio)carbonil]-6-metilpiridin-2-il}piperidin-4-carboxílico

Una mezcla de ácido piperidin-4-carboxílico (0.362 g, 2.80 mmol), S-etil 6-cloro-5-ciano-2-metilpiridin-3-carbotioato (0.674 g, 2.80 mmol) y DIPEA (0.5 mL, 2.87 mmol) en DMF (10 mL) se calentó a 100 grados durante 5 minutos usando un horno microondas de nodo simple. Se agregó NH4Cl (acuoso) y la mezcla se extrajo con DCM (3 veces). La fase orgánica combinada se secó y se evaporó para proporcionar un producto crudo, el cual se purificó mediante HPLC de fase inversa (Kromasil C8, columna 21.5 x 250 mm, caudal 25 mL/minuto, empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) para producir ácido 1-{3-ciano-5-[(etiltio)carbonil]-6-metilpiridin-2-il}piperidin-4-carboxílico. Rendimiento: 0.453 g (48% en tres pasos).

^{1}H NMR (500MHz, DMSO-d_6): 1.27 (3h, t, J = 7.3 Hz), 1.56-1.65 (2H, m), 1.92-1.98 (2H, m), 2.28 (3H, s), 2.57-2.64 (1H, m), 2.98 (2H, q, J = 7.3 Hz), 3.24-3.28 (2H, m), 4.42-4.48 (2H, m), 8.28 (1H, s), 12.31 (1H, bs).

(c) S-Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilpiridin-3-carbotioato

TBTU (0.104 g, 0.324 mmol) y DIPEA (0.1 mL, 0.574 mmol) se agregaron a una solución de ácido 1-{3-ciano-5-[(etiltio)carbonil]-6-metilpiridin-2-il} piperidin-4-carboxílico (0.090 g, 0.270 mmol) en DCM (4 mL) a temperatura de la sala y la reacción se agitó durante 45 minutos antes de agregar 1- fenilmetanosulfonamida (0.055 g, 0.321 mmol) y la agitación se continuó durante 15 horas más. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM (3 veces). La fase orgánica combinada se secó y se concentró. La evaporación, seguida por purificación mediante HPLC de fase inversa (Kromasil C8, columna 21.5 x 250 mm, caudal 25 mL/minuto, empleando una gradiente de 0.1 M NH_4OAc y CH_3CN) produjo S-etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilpiridin-3-carbotioato.

Rendimiento: 0.053 g (40%).

^{1}H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J =7.5), 1.65 (2H, m), 1.85 (2H, m), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J =7.5), 3.16 (2H, m), 4.55 (2H, m), 4.70 (2H, s), 7.30 (2H, m), 7.41 (3H, m), 8.31 (1H, s), 11.61 (1H, s). MS $^m/_z$: 487 (M+1), 485 (M-1).

Ejemplo 102

S-Etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]piridin-3-carbotioato

Preparado en la misma forma como se describe en Ejemplo 101 reemplazando fenilmetanosulfonamida por 1-(4-metilfenil)metanosulfonamida. Rendimiento: 0.065 g (48%).

^{1}H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J =7.5), 1.65 (2H, m), 1.85 (2H, m), 2.31 (3H, s), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J =7.5), 3.16

(2H, m), 4.55 (2H, m), 4.64 (2H, s), 7.17 (2H, m), 7.22 (2H, m), 8.31 (1H, s), 11.56 (1H, s). MS $^{m}/_{z}$: 501 (M+1), 499 (M-1).

Ejemplo 103

S-Etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilpiridin-3-carbotioato

Preparado en la misma forma como se describe en Ejemplo 101 reemplazando fenilmetanosulfonamida por 1-(4-clorofenil) metanosulfonamida. Rendimiento: 0.061 g (43%).

^{1}H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J =7.5), 1.65 (2H, m), 1.86 (2H, m), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J =7.5), 3.16 (2H, m), 4.55 (2H, m), 4.72 (2H, s), 7.31 (2H, m), 7.49 (2H, m), 8.31 (1H, s), 11.63 (1H, s). MS $^{m}/_{z}$: 521 (M+1), 519 (M-1).

Ejemplo 104

S-Etil 6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilpiridin-3-carbotioato

Preparado en la misma forma como se describe en Ejemplo 101 reemplazando fenilmetanosulfonamida por 1-(4-fluorofenil) metanosulfonamida. Rendimiento: 0.058 g (43%).

^{1}H NMR (500MHz, DMSO-d_6): 1.26 (3H, t, J =7.4), 1.64 (2H, m), 1.86 (2H, m), 2.56 (3H, s), 2.59 (1H, m), 3.00 (2H, q, J =7.5), 3.16 (2H, m), 4.55 (2H, m), 4.70 (2H, s), 7.25 (2H, m), 7.34
(2H, m), 8.31 (1H, s), 11.62 (1H, s). MS $^{m}/_{z}$: 505 (M+1), 503 (M-1).

Ejemplo 105

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-metoxi-2-metilnicotinato

(a) Etil 5-metoxi-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

LiH (0.0223 g, 2.80 mmol) se agregó a una solución enfriada (0°C) de etil 5-hidroxi-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (0.502 g, 2.55 mmol) en DMF (15 mL) y la mezcla resultante se agitó durante 1.5 horas. Se agregó yodometano (0.175 mL, 2.80 mmol) y la reacción se calentó a 60°C durante 20 horas. Luego de enfriar a temperatura de la sala, la mezcla se diluyó con EtOAc (200 mL), se lavó con NH_4Cl saturado (3 x 100 mL), salmuera, se secó ($MgSO_4$) y se pasó a través de gel de sílice. Cromatografía instantánea (1:1 EtOAc/hexanos) suministró etil 5-metoxi-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido. Rendimiento: 0.140g (26%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 2.68 (3H, s), 3.88 (3H, s), 4.33 (2H, q, J = 7.1 Hz), 7.31 (1H, s), 12.07 (1H, br s). MS $^m/_z$: 212 (M+1).

(b) Etil 6-cloro-5-metoxi-2-metilnicotinato

Una suspensión de etil 5-metoxi-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (0.065 g, 0.31 mmol) en $POCl_3$ (15 mL) se calentó a 60°C durante 6 horas. Luego de enfriar a temperatura de la sala, la mezcla de reacción se concentró bajo presión reducida, se diluyó con EtOAc (100 mL), se lavó con $NaHCO_3$ saturado (2 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se pasó a través de gel de sílice. La concentración proporcionó etil 6-cloro-5-metoxi-2-metilnicotinato. Rendimiento: 0.049 g (69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, t, J = 7.1 Hz), 2.74 (3H, s), 3.95 (3H, s), 4.40 (2H, q, J = 7.1 Hz), 7.71 (1H, s). MS $^m/_z$: 230 (M+1).

(c) Ácido 1-(5-(etoxicarbonil)-3-metoxi-6-metilpiridin-2-il)azetidin-3-carboxílico

Una mezcla de etil 6-cloro-5-metoxi-2-metilnicotinato (0.045 g, 0.20 mmol), ácido azetidin-3-carboxílico (0.0258 g, 0.255 mmol) y DIPEA (0.205 mL, 1.18 mmol) in NMP (2.0 mL) se calentó a 110°C durante 4 días. Luego de enfriar a temperatura de la sala, la mezcla de reacción se diluyó

con EtOAc (100 mL), se lavó con NH_4Cl saturado (3 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se concentró. Cromatografía instantánea (35% EtOAc/hexanos con 1% HOAc) proporcionó ácido 1-(5-(etoxicarbonil)-3-metoxi-6-metilpiridin-2-il)azetidin-3-carboxílico.
MS $^m/_z$: 295 (M+1).

(d) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-metoxi-2-metilnicotinato

Una solución de ácido 1-(5-(etoxicarbonil)-3-metoxi-6-metilpiridin-2-il) azetidin-3-carboxílico (0.0550 g, 0.187 mmol), fenilmetanosulfonamida (0.352 g, 0.206 mmol), EDCI (0.0394 g, 0.206 mmol), HOBt x H_2O (0.0315 g, 0.206 mmol) y DIPEA (0.0977 mL, 0.561 mmol) en DCM (2.0 mL) se agitó a temperatura de la sala durante 18 horas. La mezcla de reacción se diluyó con EtOAc (60 mL), se lavó con NH_4Cl saturado (30 mL), salmuera (50 mL), se secó ($MgSO_4$) y se concentró. Cromatografía instantánea (1:4 EtOAc / hexanos con 1% AcOH) suministró etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-metoxi-2-metilnicotinato como un sólido. Rendimiento: 0.025 g (28%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.24-3.31 (1H, m), 3.77 (3H, s), 4.21-4.35 (6H, m), 4.65 (2H, s), 7.36-7.41 (5H, m), 7.44 (1H, s). MS $^m/_z$: 448 (M+1).

Ejemplo 106

Etil 6-[4-({[(bencilsulfonil)amino]carbonil}amino)piperidin-1-il]-5-ciano-2-metilnicotinato

(a) Etil 6-(4-(terc-butoxicarbonilamino)piperidin-1-il)-5-ciano-2-metilnicotinato

Etil 6-cloro-5-cianonicotinato (2.00 g, 8.90 mmol) y *terc*-butil piperidin-4-ilcarbamato (1.78 g, 8.90 mmol) se disolvieron en EtOH (50 mL) a temperatura de la sala. Se agregó DIPEA (4.65 mL, 26.7 mmol) y el sistema se calentó a 94 °C durante 4 horas. La mezcla de reacción se enfrió a temperatura de la sala y el disolvente se concentró bajo presión reducida.

El material se repartió en porciones entre EtOAc (50 mL) y NH_4Cl acuoso saturado (2 x 30 mL). Los orgánicos se lavaron con salmuera (30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. No se efectuó purificación. Rendimiento: 3.30 g (95.4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 7.1 Hz), 1.46 (11H, s), 2.05-2.14 (2H, m), 2.72 (3H, s), 3.15-3.26 (2H, m), 3.71-3.83 (1H, m), 4.32 (2H, q, J = 7.1 Hz), 4.42-4.51 (1H, m), 4.58-4.67 (2H, m), 8.34 (1H, s). MS $^m/_z$: 389 (M+1).

(b) Diclorhidrato de etil 6-(4-aminopiperidin-1-il)-5-ciano-2-metilnicotinato

Etil 6-(4-(*terc*-butoxicarbonilamino)piperidin-1-il)-5-ciano-2-metilnicotinato (3.30 g. 8.50 mmol) se disolvió HCl (4 M en dioxano, 31.9 mL, 127 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 48 horas y se concentró bajo presión reducida para proporcionar diclorhidrato de etil 6-(4-aminopiperidin-1-il)-5-ciano-2-metilnicotinato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.

^{1}H NMR (400 MHz, d_6-DMSO): δ 1.31 (3H, t, J = 7.1 Hz), 1.53-1.68 (2H, m), 2.02-2.12 (2H, m), 2.65 (3H, s), 3.14-3.27 (2H, m), 3.30-3.43 (1H, m), 4.25 (2H, q, J = 7.1 Hz), 4.50-4.60 (2H, m), 8.17-8.29 (2H, m), 8.37 (1H, s). MS $^m/_z$: 362 (M+1).

(c) Etil 6-[4-({[(bencilsulfonil)amino]carbonil}amino)piperidin-1-il]-5-ciano-2-metilnicotinato

CDI (0.152 g, 0.934 mmol) y 1-fenilmetanosulfonamida (0.200 g, 1.17 mmol) se disolvieron en DCE (2 mL) y se agitaron durante 16 horas a temperatura de la sala. Se agregaron diclorhidrato de etil 6-(4-aminopiperidin-1-il)-5-ciano-2-metilnicotinato (0.200 g, 0.554 mmol) en DCE (2 mL) y DIPEA (0.482 mL, 2.77 mmol) a esta solución y se agitaron a temperatura de la sala durante 5 horas. La mezcla de reacción se

concentró bajo presión reducida y se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con 2 N HCl (2 x 30 mL), NH_4Cl saturado (2 x 30 mL), y agua (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Trituración (40% hexanos, 40% Et_2O, y 20% DCM) produjo etil 6-[4-({[(bencilsulfonil)amino]carbonil}amino)piperidin-1-il]-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.185 g (68.8%).
^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.1 Hz), 1.39-1.56 (2H, m), 1.88-2.00 (2H, m), 2.64 (3H, s), 3.77-3.89 (1H, m), 4.25 (2H, q, J = 7.1 Hz), 4.39-4.49 (2H, m), 4.69 (2H, s), 6.32-6.41 (1H, m), 7.29-7.45 (5H, m), 8.34 (1H, s), 9.90 (1H, s). MS $^m/_z$: 486 (M+1).

Ejemplo 107

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperazin-1-il)-5-ciano-2-metilnicotinato

(a) *terc*-Butil 4-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il] piperazin-1-carboxilato

Etil 6-cloro-5-cianonicotinato (0.500 g, 2.23 mmol) y *terc*-butil piperazin-1-carboxilato (0.623 g, 3.35 mmol) se disolvieron en EtOH (50 mL) a temperatura de la sala. Se agregó DIPEA (1.16 mL, 6.68 mmol) y el sistema se calentó a 55 °C durante 6 horas. La mezcla de reacción se enfrió a temperatura de la sala y el disolvente se concentró bajo presión reducida. El material se repartió en porciones entre EtOAc (50 mL) y NH_4Cl acuoso saturado (2 x 30 mL). Los orgánicos se lavaron con salmuera (30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Cromatografía instantánea (20% EtOAc en hexanos) produjo *terc*-butil 4-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il) piperazin-1-carboxilato. Rendimiento: 0.743 g (89.2%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (3H, q, J = 7.1 Hz), 1.49 (9H, s), 2.73 (3H, s), 3.53-3.61 (4H, m), 3.86-3.95 (4H, m), 4.32 (2H, q, J = 7.1 Hz), 8.36 (1H, s). MS $^m/_z$: 375 (M+1).

(b) Diclorhidrato de etil 5-ciano-1-metil-6-piperazin-1-ilnicotinato

terc-Butil 4-(3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il)piperazin-1-carboxilato (3.30 g. 8.50 mmol) se disolvió en HCl (2 M en Et_2O, 2.98 mL, 5.95 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 24 horas y se concentró bajo presión reducida para proporcionar diclorhidrato de etil 5-ciano-2-metil-6-(piperazin-1-il)nicotinato como un sólido, el cual se utilizó crudo asumiendo una conversión del 100%.
^{1}H NMR (400 MHz, CD_3OD): δ 1.31 (3H, t, J = 7.1 Hz), 2.67 (3H, s), 3.19-3.30 (4H, m), 3.99-4.09 (4H, m), 4.27 (2H, q, J = 7.1 Hz), 8.43 (1H, s), 9.28 (1H, m). MS $^m/_z$: 275 (M+1).

(c) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperazin-1-il)-5-ciano-2-metilnicotinato

CDI (0.152 g, 0.934 mmol) y 1-fenilmetanosulfonamida (0.200 g, 1.17 mmol) se disolvieron en DCE (2 mL) y se agitaron durante 16 horas a temperatura de la sala. Se agregaron diclorhidrato de etil 5-ciano-2-metil-6-(piperazin-1-il)nicotinato (0.200 g, 0.576 mmol) in DCE (2 mL) y DIPEA (0.502 mL, 2.88 mmol) a esta solución y se agitaron a temperatura de la sala durante 5 horas. La mezcla de reacción se concentró bajo presión reducida y se diluyó con EtOAc (40 mL). Los orgánicos combinados se lavaron con 2M HCl (2 x 30 mL), NH_4Cl saturado (2 x 30 mL), y H_2O (2 x 30 mL), se secaron ($MgSO_4$) y se concentraron bajo presión reducida para proporcionar el producto crudo. Trituración (40% hexanos, 40% Et_2O, y 20% DCM luego 10% MeOH en Et_2O) produjo etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperazin-1-il)-5-ciano-2-metilnicotinato como un sólido. Rendimiento: 0.156 g (57%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.31 (3H, t, J = 7.1 Hz), 2.66 (3H, s), 3.52-3.62 (4H, m), 3.80-3.90 (4H, m), 4.26 (2H, q, J = 7.1 Hz), 4.76 (2H, s), 7.33-7.42 (5H, m), 8.35 (1H, s), 10.5-10.6 (1H, m). MS $^m/_z$: 472 (M+1).

Ejemplo 108

Ácido 4-{[2-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico

Una solución de etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato (0.050 g, 0.089 mmol) en THF (4 mL) se enfrió a 0°C y se trató con NaOH (1.00 M, 0.18 mL, 0.18 mmol). La reacción se calentó a temperatura de la sala y se agitó durante 18 horas. Luego de la dilución con EtOAc (100 mL), la mezcla se lavó con NH_4Cl saturado (2 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$), y se concentró. Cromatografía instantánea (50% EtOAc/hexanos con 1% HOAc) suministró ácido 4-{[2-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico como un sólido. Rendimiento: 0.036 g (67%). MS $^m/_z$: 548 (M+1).

Ejemplo 109

Etil 5-ciano-2-metil-6-{3-[({[(1-oxidopiridin-2-il)metil]sulfonil}amino) carbonil]azetidin-1-il}nicotinato

a) 1 -Piridin-2-ilmetanosulfonamida

A una solución de SMOPS (4.8 g, 0.028 mol) en DMSO (seco, 50 mL) se agregó HBr de 2-bromometilpiridina (5 g, 0.019 mol) a temperatura de la sala. Después de 40 minutos, se ajustó el pH de la solución a 8 mediante la adición de una solución de bicarbonato acuoso. La mezcla de reacción se extrajo con EtOAc (4 x 100 mL), las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro, se filtraron y los disolventes se retiraron *in vacuo*. El residuo se re-disolvió en una mezcla de disolventes compuestos por THF (200 mL) y metanol (10 mL) y se trataron con una solución de de metóxido de sodio (4 mL, 25%) durante un período de 10

minutos. Después de agitar durante 40 minutos, la mezcla de reacción se concentró *in vacuo* y se disolvió en agua (20 mL), seguida por la adición de una solución de ácido hidroxilamin-O-sulfónico (12.66 g, 0.099 mol), acetato de sodio (7g) en agua (60 mL), seguida por agitación a temperatura de la sala. Después de 48 horas, se ajustó el pH de la solución a 9 mediante la adición de solución de bicarbonato acuoso y la mezcla se sometió a secamiento por congelamiento. El sólido así obtenido se trató con metanol, la capa metanólica se separó y se concentró. El residuo se purificó por cromatografía instantánea en sílice empleando una gradiente de EtOAc en éter de petróleo, seguido por EtOAc y luego con MeOH en EtOAc para producir 1-piridin-2-ilmetanosulfonamida. Rendimiento: 400 mg (12%).
^{1}H NMR (400 MHz, DMSO-d6) δ 4.42-4.45 (2H, m), 6.90-6.95 (2H, m), 7.33-7.39 (1H, m), 7.45-7.50(1H, m), 7.78-7.85 (1H, m), 8.53-8.59 (1H, m).
MS $^m/_z$: 173 (M+1).

b) 1-(1-oxidopiridin-2-il)metanosulfonamida

1-Piridin-2-ilmetanosulfonamida (100 mg, 0.55 mmol) se disolvió en DCM (2mL) y se enfrió en un baño helado antes de agregar m-CPBA (184 mg, 0.61 mmol) disuelto en DCM (1ml). La reacción se agitó a temperatura de la sala durante 2 horas, seguida por retiro de los disolventes *in vacuo*. El sólido crudo se disolvió en CH_3CN/H_2O(4 mL), y se purificó en HPLC preparativa (C8, 10 um, 20x250 mm) 25ml/minuto, 5% CH_3CN en 0.2% HOAc. Se aisló 1-(1-oxidopiridin-2-il)metanosulfonamida como un sólido amarillo claro. Rendimiento = 65mg (60%). MS $^m/_z$: 189 (M+1).

c) Etil 5-ciano-2-metil-6-{3-[({[(1-oxidopiridin-2-il)metil]sulfonil} amino) carbonil]azetidin-1-il}nicotinato

Preparado de acuerdo con el método B a partir de 1-(1-oxidopiridin-2-il) metanosulfonamida. Rendimiento = 13 mg (14%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 2.63 (3H, s), 3.40 - 3.53 (1H, m), 4.23 (2H, q, J = 7.1 Hz), 4.31 - 4.51 (4H, m), 5.02 (2H,

s), 7.27 - 7.49 (2H, m), 7.57 - 7.69 (1H, m), 8.20 - 8.25 (1H, m),8.29 (1H, s). MS $^{m}/_{z}$: 460 (M+1).

Ejemplo 110

Etil 5-ciano-2-metil-6-[3-({[(piridin-3-ilmetil)sulfonil]amino} carbonil) azetidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 1-piridin-3-ilmetanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109, paso a. Rendimiento = 6 mg (7%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, *J* = 6.9 Hz), 2.63 (3H, s), 3.38 - 3.49 (1H, m), 4.23 (2H, q, *J* = 7.0 Hz), 4.28 - 4.55 (4H, m), 4.64 (2H, s), 7.30 - 7.48 (1H, m), 7.66 - 7.83 (1H, m), 8.29 (1H, s), 8.47 (1H, s), 8.50 - 8.57 (1H, m). MS $^{m}/_{z}$: 444 (M+1).

Ejemplo 111

Etil 5-ciano-2-metil-6-{4-[({[(1-oxidopiridin-2-il)metil]sulfonil} amino) carbonil]piperidin-1-il}nicotinato

Preparado de acuerdo con el método B a partir de 1-(1-oxidopiridin-2-il) metanosulfonamida (véase Ejemplo 109 a y b). Rendimiento = 27 mg (28%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, *J* = 7.2 Hz), 1.56 - 1.72 (2H, m), 1.86 - 1.99 (2H, m), 2.47 - 2.55 (1H, m), 2.64 (3H, s), 3.12 - 3.24 (2H, m), 4.25 (2H, q, *J* = 7.1 Hz), 4.45-4.60 (2H, m), 5.02 (2H, s), 7.30 - 7.49 (2H, m), 7.55-7.65 (1H, m), 8.25-8.37 (2H, m), 11.62 - 11.92 (1H, m). MS $^{m}/_{z}$: 488 (M+1).

Ejemplo 112

Etil 5-ciano-2-metil-6-[4-({[(piridin-3-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 1-piridin-3-ilmetanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al ejemplo 109, paso a. Rendimiento = 32 mg (34%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.55-1.71 (2H, m), 1.79 - 1.89 (2H, m), 2.46 - 2.56 (1H, m), 2.65 (3H, s), 3.09 - 3.21 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.49 - 4.59 (2H, m),4.73 (2H, s), 7.38 - 7.50 (1H, m), 7.66 - 7.78 (1H, m), 8.34 (1H, s), 8.47 (1H, s), 8.52 - 8.62 (1H, m), 11.58 - 11.85 (1H, m). MS $^m/_z$: 472 (M+1).

Ejemplo 113

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(dimetilamino)nicotinato

a) Etil 5-ciano-6-hidroxi-2 -oxo-1,2-dihidropiridin-3-carboxilato

Na (2.76 g, 120 mmol) se agregó gradualmente a 22 mL de etanol y se calentó a 80°C durante 45 minutos. Esto se agregó a una suspensión de 2-cianoacetamida (4.2 g, 50 mmol) en 6 mL de etanol caliente. La mezcla se agitó durante 20 minutos, seguida por la adición de dietil (etoximetilen) malonato (10.8 g, 50 mmol). La mezcla de reacción se hizo refluir durante 16 horas, seguida por enfriamiento a temperatura ambiente. El producto crudo se extrajo completamente por filtración y el material sólido se trituró con 2x20 mL éter dietílico, seguido por 2x20 mL de heptano. El sólido se secó bajo vacío para producir etil 5-ciano-6-hidroxi-2-oxo-1,2-dihidropiridin-3-carboxilato.

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.05 (3H, t, J =7Hz), 3.40 (2H, d, J =7Hz), 7.88 (1H, s).

b) Etil 2,6-dicloro-5-cianonicotinato

A etil 5-ciano-6-hidroxi-2-oxo-1,2-dihidropiridin-3-carboxilato (1.56 g, 7.50 mmol) en tolueno 15b mL se agregó cloruro de tionilo (5.35 g, 45 mmol), seguido por DMF (55 mg, 75 mmol). La mezcla de reacción se calentó a 85 °C durante 16 horas. Se agregó una cantidad adicional de cloruro de tionilo (5.35 g, 45 mmol), seguido por DMF (55 mg, 75 mmol),

seguido por calentamiento a 100 °C durante 4 horas. Los disolventes se retiraron *in vacuo* para una parte del material, el cual se utilizó en el paso consecutivo.

c) Etil 6-cloro-5-ciano-2-(dimetilamino)nicotinato

Etil 2,6-dicloro-5-cianonicotinato (147 mg, 0.600 mmol) en 1.5 mL MeCN se enfrió a 0 °C, seguido por la adición *N*-metilmetanamina (10.5 µL, 0.150 mmol) en 0.15 mL MeCN, agitando a 0 °C durante 15 minutos, seguido por la adición de una cantidad adicional de *N*-metilmetanamina (10.5 µL, 0.150 mmol) en 0.15 mL. La mezcla de reacción se agitó a temperatura de la sala durante 16 horas. Los disolventes se retiraron *in vacuo* y parte del material se utilizó inmediatamente en el siguiente paso.

d) Ácido 1-[3-ciano-6-(dimetilamino)-5-(etoxicarbonil)piridin-2-il] piperidin-4-carboxílico

Etil 6-cloro-5-ciano-2-(dimetilamino)nicotinato (76 mg, 0.300 mmol) del paso anterior se disolvió en 1.5 mL etanol/agua 1:1, seguidos por la adición de ácido piperidin-4-carboxílico (116 mg, 0.90 mmol), seguido por TEA (91 mg, 0.90 mmol). La mezcla de reacción se calentó en un horno microondas de nodo simple a 120°C durante 20 minutos. Los disolventes se retiraron *in vacuo* para producir 201mg de material crudo.

La purificación se efectuó mediante HPLC de fase inversa. A: MeCN, B: 0.1 M acetato de amonio MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado con un caudal = 10 mL/minuto. Se incrementó a caudal = 50 mL/minuto continuo durante 3 minutos después de la inyección. Luego se cambió a A/B/C 5:0:95 y se aumentó el caudal a 100 mL/min. Se incrementó a 100:0:0 durante 17 minutos en pasos de puntos de 5%. Columna: Kromasil C8, 250 mm x 50.8 ID. El producto se eluyó cuando A/C fue de 70:30. Esto produjo ácido 1-[3-ciano-6-(dimetilamino)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico. Rendimiento = 44 mg (42%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35(3H, t, *J* =7.0Hz), 1.78-1.89(2H, m), 1.99-2.01 (2H, m), 2.61-2.67 (1H, m), 3.3-3.5 (6H, m), 3.17-3.24 (2H, m), 4.28 (2H, q, 7.0Hz), 4.42-4.49 (2H, m), 8.13 (1H, s).

e) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(dimetilamino)nicotinato

Ácido 1-[3-ciano-6-(dimetilamino)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico (24 mg, 0.069 mmol) se disolvió en DCM(1mL), seguido por la adición de TBTU (37 mg, 0.097 mmol) y DIPEA (0.047 mL, 0.28 mmol). Después de 2 minutos se agregó1-fenilmetanosulfonamida (14 mg, 0.083 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 6 horas, seguida por la adición 0.094 mL DIPEA. Se continuó la agitación a temperatura de la sala durante 16 horas más. Se agregaron 1-fenilmetanosulfonamida (14 mg, 0.083 mmol) y TBTU (37 mg, 0.097 mmol), seguidas por agitación a temperatura de la sala durante 22 horas más. La purificación se efectuó mediante HPLC de fase inversa: A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 10 mL/min. Incrementado a caudal = 20 mL/minuto, justo después de la inyección. Luego se cambió a A/B/C 5:0:95. Se incrementó a 50:0:50 durante 30 minutos en 9 pasos iguales. Luego a 100:0:0 durante 10 minutos en 5 pasos. Caudal: 20 mL/minuto. Columna: Kromasil C8, 250 mmx20 ID. Esto produjo etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(dimetilamino)nicotinato. Rendimiento = 8 mg (23%).

^{1}H NMR (500 MHz, $CDCd_6$): δ 1.35 (3H, t, *J* = 7.2 Hz), 1.71-1.86 (4H, m), 2.33-2.42 (1H, m), 2.98-3.04 (2H, m), 3.05 (6H, s), 4.28 (2H, q, *J* = 7.2 Hz), 4.48-4.54 (2H, m), 4.65 (2H, s), 7.31-7.35 (2H, m), 7.36-7.43 (3H, m), 8.12 (1H, s). MS $^m/_z$: 500 (M+1).

Ejemplo 114

Etil 5-ciano-2-metil-6-[4-({[(piridin-4-ilmetil)sulfonil]amino} carbonil) piperidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 1-piridin-4-ilmetanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109, paso a. Rendimiento = 20 mg (21%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.56 - 1.70 (2H, m), 1.79 - 1.89 (2H, m), 2.46 - 2.56 (1H, m), 2.65 (3H, s), 3.08 - 3.21 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.48 - 4.58 (2H, m), 4.73 (2H, s), 7.29-7.33 (2H,m), 8.34 (1H, s), 8.58-8.62 (2H, m), 11.65-11.93 (1H, m). MS $^m/_z$: 472 (M+1).

Ejemplo 115

Etil 5-ciano-2-metil-6-[3-({[(piridin-2-ilmetil)sulfonil]amino} carbonil) azetidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 1-piridin-2-ilmetanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109, paso a. Rendimiento = 7 mg (8%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 2.64 (3H, s), 3.43 - 3.57 (1H, m), 4.24(2H, q, J = 7.1 Hz), 4.36 - 4.56 (4H, m), 4.80 (2H, s), 7.30 - 7.57 (2H, m), 7.75-7.89 (1H, m), 8.31(1H, s), 8.49 - 8.59 (1H, m), 11.52 - 11.99 (1H, m). MS $^m/_z$: 444 (M+1).

Ejemplo 116

Etil 5-ciano-6-[3-({[(3,5-dimetilbencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-(3,5-dimetilfenil) metanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109. Rendimiento = 5 mg (5%). MS $^m/_z$: 471 (M+1).

Ejemplo 117

Isopropil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

A ácido 1-[3-ciano-5-(isopropoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (100 mg, 0.301 mmol) se agregaron TBTU (97mg, 0.302 mmol), DCM seco (2mL), DIPEA (0.1mL, 0.574 mmol) y la mezcla se agitó a temperatura de la sala durante 2.5 horas. La mezcla se agregó a 1-ciclopentilmetanosulfonamida (58.8mg, 0.360 mmol), se agregó DCM seco (2ml) y la mezcla de reacción se agitó a temperatura de la sala durante 18 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo tres veces con DCM. Las capas orgánicas combinadas se pasaron por un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8 10µm, 21.5x250 mm) empleando una gradiente de 25-55% acetonitrilo/amortiguador NH4OAc acuoso pH 7 para producir isopropil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato. Rendimiento: 80 mg (56%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22-1.93 (12H, m), 1.30 (6H, app d, *J* =6.2Hz), 2.11-2.20 (1H, m), 2.64 (3H, s), 2.64-2.69 (1H, m), 3.14-3.21 (2H, m), 3.42 (2H, d, *J =7.0 Hz*), 4.51- 4.57 (2H, m), 5.08 (1H, app q, *J* =6.2Hz), 8.32 (1H, s), 11.71 (1H, s). MS $^m/_2$: 477.3 (M+1), 475.3 (M-1).

Ejemplo 118

Etil 5-ciano-6-[4-({[(2,5-dimetilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-(2,5-dimetilfenil) metanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109. Rendimiento = 18 mg (18%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, *J* = 7.1 Hz), 1.59 - 1.76 (2H, m), 1.83 - 1.95 (2H, m), 2.25 (3H, s), 2.33 (3H, s), 2.47 - 2.56 (1H, m), 2.65 (3H, s), 3.11 - 3.23 (2H, m), 4.25 (2H, q, *J* = 7.1 Hz), 4.51 - 4.60 (2H, m), 4.64 (2H, s), 6.95 (1H, s), 7.04 - 7.15 (2H, m), 8.34 (1H, s), 11.54 - 11.87 (1H, m). MS $^m/_z$: 499 (M+1).

Ejemplo 119

Etil 5-ciano-6-[4-({[(4-isopropilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

a) (4-Isopropilfenil)metanosulfonato de sodio

1-(Clorometil)-4-isopropilbenceno (2.53 g, 15.0 mmol) y sulfito disódico (2.46, 19.5 mmol) se agregaron a una mezcla de agua (8mL) y acetona (0.8mL). La mezcla de reacción se calentó, en un horno microondas, calentamiento de nodo simple, a 150 grados durante 5 minutos. La mezcla de reacción se transfirió a un matraz de base redonda con acetona (40mL) y agua (4mL). La mezcla se hizo refluir durante 5.5 horas. Los disolventes se retiraron *in vacuo* y los sólidos remanentes se suspendieron en 20 mL de etanol absoluto caliente y los cristales se extrajeron completamente por filtración. La torta filtrante se enjuagó con 10 mL etanol absoluto, seguido por 2x15 mL heptano y, finalmente, se secó bajo vacío durante 2 horas. Esto produjo (4-isopropilfenil)metanosulfonato de sodio. Rendimiento = 3.3 g (92%).

b) 1-(4-Isopropilfenil)metanosulfonamida

(4-Isopropilfenil)metanosulfonato de sodio (1.9 g, 8.0 mmol), seguido por dioxano (32mL) y cloruro de tionilo (2.92 mL, 40 mmol) se distribuyó en 4 frascos y se calentó a 100°C durante 20 minutos, empleando cada uno un tiempo fijo de permanencia. Las mezclas de reacción se combinaron y los disolventes se retiraron *in vacuo*. Una solución de amoníaco en THF (40 mL) se agregó a temperatura de la sala y la mezcla de reacción se agitó durante 16 horas. Se agregó agua (30mL) y la fase orgánica se separó. La fase acuosa se extrajo con 2x30 mL acetato de etilo. Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y los disolventes se retiraron *in vacuo*. El crudo se purificó mediante cromatografía instantánea en gel de sílice con heptano/acetato de etilo 2:1 (Rf de producto

= 0.22) como eluyente para producir 1-(4-isopropilfenil) metanosulfonamida. Rendimiento = 376 mg, 1.76 mmol. (22%).

c) Etil 5-ciano-6-[4-({[(4-isopropilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (159 mg, 0.500 mmol) se disolvió en DCM (4mL) y se agregó HATU (265 mg, 0.700 mmol)), seguido por DIPEA (0.341 mL, 2mmol). La mezcla de reacción se agitó a temperatura de la sala durante 5 minutos antes de la adición de 1-(4-isopropilfenil)metanosulfonamida (128 mg, 0.600mmol). Se continuó la agitación durante 18 horas. La mezcla de reacción se concentró y luego se disolvió en DMSO (8mL).

La purificación se efectuó mediante HPLC de fase inversa. A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 10 mL/minuto. Incrementado a un caudal = 50 mL/minuto continuo durante 3 minutos después de la inyección. Luego se cambió a A/B/C 5:0:95 y el caudal se aumentó a 100 mL/minuto. Incrementado a 100:0:0 durante 17 minutos en pasos iguales, cada uno de puntos de 5%. El producto se eluyó cambiando a acetonitrilo puro. Columna: Kromasil C8, 250 mm x 50.8 ID. Esto produjo etil 5-ciano-6-[4-({[(4-isopropilbencil)sulfonil]amino} carbonil)piperidin-1-il]-2-metilnicotinato. Rendimiento: 0.144 g (56%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.18 (6H, d, J = 6.8 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.54-1.67 (2H, m), 1.75-1.85 (2H, m), 2.20-2.30 (1H, m), 2.65 (3H, s), 2.80-2.89 (1H, m), 3.18-3.28 (2H, m), 4.19 (2H, s), 4.26 (2H, q, J = 7.1 Hz), 4.38-4.47 (2H, m), 7.09-7.18 (4H, m), 8.32 (1H, s). MS $^m/_z$: 513 (M+1).

Ejemplo 120

Bencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

a) 1-(4-Metilfenil)metanosulfonamida

A una solución agitada de SMOPS (5.646 g, 0.0324 mol) en DMSO (seco, 50 mL) se agregó α-bromo-p-xileno (5 g, 0.027 mol) a temperatura de la sala y la agitación se continuó durante 45 minutos. La mezcla de reacción se extrajo con EtOAc (4 x 100 mL), las capas orgánicas se combinaron, se secaron sobre sulfato de sodio anhidro y los disolventes se retiraron *in vacuo*. El residuo se re-disolvió en THF (100 mL) y metanol (25 mL), seguidos por la adición de metóxido de sodio (5.8 mL, 0.027 mol, 25%). Después de agitar durante 15 minutos, la mezcla de reacción se concentró y se disolvió en agua (10 mL). Una solución de ácido hidroxilamin-O-sulfónico (17.31g, 0.1350 mol) y acetato de sodio (7g) en H_2O (40 mL) se agregó a la mezcla de reacción, la cual se agitó a temperatura de la sala durante 12 horas. Se ajustó el pH de la solución a 9 mediante la adición de solución de bicarbonato acuoso y la mezcla se extrajo con EtOAc (3x50 ml), se lavó con salmuera, se secó (Na_2SO_4), y los disolventes se retiraron *in vacuo*. El residuo así obtenido se trató con agua (100 mL) y se agitó durante 10 minutos. El sólido obtenido se filtró y se secó para proporcionar 1-(4-metilfenil)metanosulfonamida. Rendimiento = 3.3 g, (66%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.55(3H, s), 4.05(2H, s), 6.8 (2H, s), 7.1-7,3 (4H, m).

b) 1-(4-Metilciclohexil)metanosulfonamida

PtO_2 (2 g) se agregó a una solución agitada de 1-(4-metilfenil) metanosulfonamida (2 g, 0.0180 mol) en ácido acético (50 mL) a temperatura de la sala en un agitador Parr y se continuó agitando durante ~ 48 horas bajo H_2 (presión a 6 kg/cm^2). Una vez completa la reacción, la mezcla de reacción se filtró, se lavó con ácido acético (30 mL) y se concentró. El producto crudo se purificó empleando cromatografía de columna instantánea con 10% EtOAc en éter de petróleo para proporcionar 1-(4-metilciclohexil)metanosulfonamida. Rendimiento = 520 mg (25.2%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83-2.2(13H, m) 2.84-2.94 (2H m), 6.74 (2H, s). MS $^m/_z$: 191.8 (M+1).

c) Etil 5-ciano-2-metil-6-{4-[({[(4-metilciclohexil)metil] sulfonil}amino) carbonil]piperidin-1-il}nicotinato

Preparado de acuerdo con el método B a partir de 1-(4-metilciclohexil) metanosulfonamida. Rendimiento = 23 mg (23%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 - 0.97 (4H, m), 0.99 - 1.21 (2H, m), 1.30 (3H, t, J = 7.2 Hz), 1.39 - 1.57 (4H, m), 1.57 - 1.73 (2H, m), 1.78 - 1.98 (3H, m), 2.00 - 2.11 (1H, m), 2.47-2.6 (1H, m), 2.64 (3H, s), 3.12 - 3.23 (2H, m), 3.22 - 3.40 (3H, m), 4.25 (2H, q, J = 7.1 Hz), 4.47 - 4.61 (2H, m), 8.33 (1H, s), 11.66 - 11.81 (1H, m). MS $^m/_z$: 491 (M+1).

Ejemplo 122

Etil 5-ciano-6-[3-({[(4-isopropilbencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (145 mg, 0.500 mmol) se disolvió en 4 mL DCM/DMF 1:1. Se agregaron HBTU (0.265,.0.700 mmol) y DIPEA (0.341mL, 2 mmol). Adicionalmente se agregó 2 mL DMF. Se agregó 1-(4-isopropilfenil)metanosulfonamida (128 mg, 0.600 mmol) y la mezcla de reacción se agitó durante 18 horas. Se agregaron más HBTU (0.095 g, 0.25 mmol) y DIPEA (0.17 mL, 1 mmol.) y se continuó la agitación a temperatura de la sala durante 22 horas. La solución se concentró y luego se disolvió en 8 mL DMSO. El producto se aisló mediante HPLC de fase inversa. A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 10 mL/minuto. Incrementado a un caudal = 50 mL/minuto continuo durante 3 minutos después de la inyección. Luego se cambió a A/B/C 5:0:95 y se sumentó el caudal a 100 mL/minuto. Se incrementó a 100:0:0 durante 17 minutos en pasos iguales, cada uno de puntos de 5%. Columna: Kromasil C8, 250 mm x 50.8 ID.

Esto produjo etil 5-ciano-6-[3-({[(4-isopropilbencil)sulfonil]amino} carbonil)azetidin-1-il]-2-metilnicotinato. Rendimiento: 0.198 g, (82%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.18 (6H, d, J = 6.9 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.63 (3H, s), 2.73-2.87 (1H, m), 3.17-3.26 (1H, m), 4.21-4.27 (4H, m), 4.27-4.48 (4H, m), 7.08 (2H, d, J = 8.1 Hz), 7.17 (2H, d, J = 8.1 Hz), 8.28 (1H, s). MS $^m/_z$: 485 (M+1).

Ejemplo 123

Etil 5-ciano-2-metil-6-[4-({[(2-feniletil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 2-feniletanosulfonamida. Rendimiento = 22 mg (22%).

^{1}H NMR (400 MHz, DMSO-d6) δ 1.30 (3H, t, J = 7.1 Hz), 1.50 - 1.65 (2H, m), 1.82 - 1.94 (2H, m), 2.50 - 2.53 (1H, m), 2.64 (3H, s), 2.93 - 3.00 (2H, m), 3.10 - 3.21 (2H, m), 3.58 - 3.70 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.46 - 4.58 (2H, m), 7.16 - 7.37 (5H, m), 8.33 (1H, s), 11.69 - 11.85 (1H, m). MS $^m/_z$: 485 (M+1).

Ejemplo 124

Etil 5-ciano-2-metil-6-[4-({[(piridin-2-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 1-piridin-2-ilmetanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109, paso a. Rendimiento = 7 mg (7%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.1 Hz), 1.61 - 1.74 (2H, m), 1.83 - 1.92 0 (2H, m), 2.47 - 2.56 (1H, m), 2.65 (3H, s), 3.13 - 3.25 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.48 - 4.58 (2H, m), 4.77 (2H, s), 7.35-7.42 (1H, m), 7.46 (1H, d, J = 7.9 Hz), 7.79 - 7.88 (1H, m), 8.34 (1H, s), 8.52 - 8.58 (1H, m), 11.41 - 11.70 (1H, m). MS $^m/_z$: 472 (M+1).

Ejemplo 125

Etil 5-ciano-6-[3-({[(2,5-dimetilbencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-(2,5-dimetilfenil)metanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109. Rendimiento = 6 mg (6%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 2.24 (3H, s), 2.34 (3H, s), 2.63 (3H, s), 3.52 - 3.68 (1H, m), 4.24 (2H, q, J = 7.1 Hz), 4.31 - 4.41 (2H, m), 4.41 - 4.51 (2H, m), 4.70 (2H, s), 7.01 (1H, s), 7.05-7.15 (2H, m), 8.31 (1H, s), 11.76 - 12.09 (1H, m). MS $^m/_z$: 471 (M+1).

Ejemplo 126

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloro-2-metilnicotinato

a) Etil 5-cloro-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

Etil 2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (2.00 g, 11.0 mmol), (Raileanu D., et. al. Tetrahedron, vol. 30 páginas 623-32, 1974) se disolvió en DMF (35 mL) bajo una atmósfera de nitrógeno. NCS (1.53g, 11.5 mmol) se tomó en DMF (5.0 mL) a temperatura de la sala. La mezcla de reacción se calentó a 100°C durante 1 hora. Se agregó una cantidad adicional de NCS (500mg, 3.8 mmol) y la mezcla de reacción se agitó durante 0.5 hora. La mezcla de reacción se diluyó con DCM, se lavó con agua y salmuera cada vez. La fase acuosa se extrajo con DCM dos veces y las fases orgánicas se combinaron, se pasaron por un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó por cromatografía instantánea en sílice (Biotage horizon) primero EtOAc/heptano 1:1, seguido por EtOAc para producir etil 5-cloro-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido amarillo. Rendimiento = 1.362 g (52%).

^{1}H NMR (400 MHz, DMSO-d_6) 5 1.37 (3H, t, J = 7.3 Hz), 2.74 (3H, s), 4.32 (2H, q, J = 7.3) Hz, 8.19 (1H, s).

b) Etil 5,6-dicloro-2-metilnicotinato

Etil 5-cloro-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (1.2g, 5.1 mmol) se disolvió en DCM (25mL), seguido por la adición de cloruro de oxalilo (2.2mL, 26 mmol). Se agregaron dos gotas de DMF y la mezcla se calentó a 42°C. Luego de 3 horas, se agregó cloruro de oxalilo (2 mL, 24 mmol). Después de 1 hora, se agregaron cloruro de oxalilo (1.1ml, 13 mmol) y DMF (0.03mL), y la mezcla de reacción se agitó a 50°C de un día para otro. La mezcla de reacción se diluyó con DCM y se virtió en una mezcla de hielo/agua. Las fases se separaron y la fase orgánica se lavó con $NaHCO_3$ x 2 saturado, seguido por salmuera. Las fases acuosas combinadas se extrajeron con DCM y las fases orgánicas combinadas se filtraron a través de un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo es co-concentró con DCM tres veces, lo cual produjo etil 5,6-dicloro-2-metilnicotinato como un sólido café oscuro. Rendimiento: 0.949g (52%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 8.0 Hz), 2.67 (3H, s), 4.32 (2H, q, J = 7.2 Hz), 8.37 (1H, s).

c) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloro-2-metilnicotinato

Etil 5,6-dicloro-2-metilnicotinato (202mg 0.846 mmol) y *N*-(bencilsulfonil)azetidin-3-carboxamida (237mg, 0.930 mmol) se disolvieron en EtOH (5mL), agua (8mL) y MeCN (3mL). Se calentó en un horno microondas, calentamiento de nodo simple, durante 20 minutos a 120°C. Se agregó TEA (0.47 mL, 3.4 mmol) y la mezcla se calentó en un horno microondas durante 20 minutos a 120°C. La mezcla de reacción se diluyó con DCM y los orgánicos se lavaron con 2% $KHSO_4$ dos veces. Las fases combinadas acuosas se extrajeron con DCM. Las fases orgánicas combinadas se pasaron a través de un separador de fase, seguidas por el retiro de los disolventes *in vacuo*. El producto crudo se purificó empleando HPLC preparativa en una columna (Kromasil C8, 50.8 x 300 mm), con el fin de evitar la precipitación, el compuesto se cargó en la columna

empelando 5% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7. El producto se eluyó empleando una gradiente de 5-90% acetonitrilo/amortiguador NH_4OAc acuoso, pH 3 para producir etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloro-2-metilnicotinato puro. Rendimiento: 204 mg (53%).

^1H NMR (400 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.3 Hz) , 2.58 (3H, s), 3.53 - 3.43 (1H, m), 4.15-4.42 (6H, m), 4.74 (2H, s), 7.25-7.43 (5H, m), 7.93 (1H, s), 11.77 (1H, s). $MS^m/_z$: 452 (M+1).

Ejemplo 127

Etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-metilnicotinato

a) Ácido azetidin-3-ilacético

Ácido [1-(*terc*-butoxicarbonil)azetidin-3-il]acético (1.0g, 4.65 mmol) se disolvió en DCM (8mL), seguido por la adición de TFA (5mL). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas. Los disolventes se retiraron y le ácido azetidin-3-ilacético crudo (1.31g, quedó TFA) se utilizó en el paso b) sin purificación.

^1H-NMR (500MHz, DMSO-d6) δ 2.61-2.65(2H, m), 2.98-3.09 (1H, m), 3.68-3.77(2H, m), 3.95-4.03(2H, m).

b) Ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-il} acético

Ácido azetidin-3-ilacético (460.5 mg, 5.00 mmol) del paso anterior se disolvió en EtOH(8mL) y se agregaron etil 6-cloro-5-ciano-2-metilnicotinato (1.02 g) y DIPEA (2mL). La mezcla de reacción se calentó a 100°C durante 5 minutos empleando calentamiento en microondas de nodo simple. Se agregó NB_4Cl (acuoso) y la mezcla se extrajo con DCM tres veces. Las capas orgánicas combinadas se corrieron a través de un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó mediante HPLC preparativa.

Columna: Kromasil C8 10µm, 50.8 x 300mm, fase móvil A: 100% AcN, fase móvil B 5%, AcN, 95% NH_4AcO (acuoso) (pH7), gradiente: 20=>60% durante 60 minutos, caudal: 50ml/minuto y UV: 280 nm.

Esto produjo ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-il}acético. Rendimiento = 526mg (43.3%).

^{1}H-NMR (500MHz, DMSO-d_6) δ 1.29 (3H, t, *J* =7.1), 2.60 (3H, s), 2.63-2.66 (2H, m). 2.93- 3.02 (1H, m), 3.95-4.05 (2H, m), 4.34 (2H, q, *J*=7.1), 4.37-4.47 (2H, m).

c) Etil 6 (3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-metilnicotinato

Ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-il} acético (130mg, 0.429 mmol), TBTU (190mg, 0.592 mmol), DIPEA (0.2mL, 1.15 mmol) se disolvieron en DCM seco (4ml) y la mezcla se agitó a temperatura de la sala durante 1 hora 20 minutos. La mezcla se agregó a 1-fenilmetanosulfonamida (100 mg, 0.584 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 25 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo tres veces con DCM. La capa orgánica combinada se pasó por un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8 10µm, 21.5 x 250mm) empleando una gradiente de 25-45% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7, para producir etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-metilnicotinato. Rendimiento = 119 mg (61%).

^{1}H-NMR (500MHz, DMSO-d_6) δ1.30 (3H, t, *J* =7.2Hz), 2.62 (3H, s), 2.69 (2H, m), 3.05 (1H, m), 4.02 (2H, m), 4.23 (2H, q, *J* =7.2Hz), 4.47 (2H, m), 4.70 (2H,s), 7.31 (2H, m), 7.41 (3H, m), 8.28 (1H, s), 11.67 (1H, s). $MS^m/_z$: 457.1 (M+1), 455.0 (M-1).

Ejemplo 128

Etil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-ciclopentilmetanosulfonamida. Rendimiento = 10 mg (10%).

MS $^{m}/_{z}$: 471 (M+1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.18 - 1.28 (2H, m), 1.30 (3H, t, J = 7.1 Hz), 1.43 - 1.53 (2H, m), 1.54 - 1.69 (4H, m), 1.80 - 1.95 (4H, m), 2.08 - 2.22 (1H, m), 2.22 (3H, s), 2.65-2.69 (1H, m), 3.11 - 3.23 (2H, m), 3.38 (2H, d, J = 6.8 Hz), 4.25 (2H, q, J = 7.1 Hz), 4.48 - 4.59 (2H, m), 8.33 (1H, s), 11.48 - 12.17 (1H, m). MS $^{m}/_{z}$: 463 (M+1).

Ejemplo 129

Etil 5-ciano-6-[3-(2-{[(4-fluorobencil)sulfonil]amino}-2-oxoetil) azetidin-1-il]-2-metilnicotinato

Ácido {1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-il} acético (130 mg, 0.43 mmol), TBTU (190mg, 0.59 mmol), DIPEA (0.2mL, 1.2 mmol) se disolvieron en DCM seco (4mL) y la mezcla de reacción se agitó a temperatura de la sala durante 1 hora 20 minutos. La mezcla se agregó a 1-(4-fluorofenil)metanosulfonamida (189 mg, 0.53 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 25 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo tres veces con DCM. Las capas orgánicas combinadas se pasaron por un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8 10μm, 21.5 x 250mm) empleando una gradiente de 25-45% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7, para producir etil 5-ciano-6-[3-(2-{[(4-fluorobencil)sulfonil] amino}-2-oxoetil)azetidin-1-il]-2-metilnicotinato. Rendimiento = 134 mg (66%).

^{1}H-NMR (500MHz, DMSO-d_6): δ 1.30 (3H, t, J =7.2Hz), 2.62 (3H, s), 2.70 (2H, m), 3.04 (1H, m), 4.02 (2H, m), 4.23 (2H, q, J =7.2Hz), 4.46 (2H, m), 4.71 (2H, s), 7.26 (2H, m), 7.35 (2H, m), 8.28 (1H, s), 11.69 (1H, s). MSH$_z$): 475.1 (M+1), 473.0 (M-1).

Ejemplo 130

Etil 5-ciano-6-[4-({[(3-fluoro-4-metilbencil)sulfonil]amino} carbonil) piperidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-(3-fluoro-4-metilfenil) metanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109, paso a. Rendimiento = 2 mg (2%).
MS $^{m}/_{z}$: 503 (M+1).

Ejemplo 131

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-metilnicotinato

a) Ácido 1-[3-cloro-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico

Etil 5,6-dicloro-2-metilnicotinato (428mg, 1.79 mmol) se disolvió en MeCN (6mL), seguido por la adición de ácido piperidin-4-carboxílico (255mg, 1.74 mmol), se agregaron agua (9mL) y TEA (1.5 mL, 10.8 mmol). La mezcla de reacción se calentó durante 15 minutos a 120°C en un horno microondas de nodo simple. Se agregaron una cantidad adicional de ácido piperidin-4-carboxílico (128mg, 0.34 mmol) y TEA (0.5 mL, 3.60 mmol) y la mezcla se calentó en un horno microondas de nodo simple durante 15 minutos a 120°C. La mezcla de reacción se diluyó con DCM y se lavó con 2%$KHSO_4$. La fase acuosa se extrajo dos veces con DCM y las fases orgánicas combinadas se filtraron a través de un separador de fase y se siguieron por el retiro de los disolventes *in vacuo*. El crudo se co-concentró con DCM para producir ácido 1-[3-cloro-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico. Rendimiento = 391 mg (60%).
^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 1.71 - 1.58 (2H, m), 1.96 - 1.85 (2H, m), 2.59 (3H, s), 3.03 - 2.91 (2H, m), 4.02 - 3.91 (2H, m), 4.24 (2H, q, J = 7.1 Hz,), 8.02 (1H, s), 12.43 - 12.07 (1H, bs).

b) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-metilnicotinato

Ácido 1-[3-cloro-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (391 mg, 1.08 mmol), DIPEA (0.9 mL, 5.4 mmol)) y TBTU (404mg, 1.25 mmol) se disolvieron en DCM seco (8 mL) y se agitaron durante 15 minutos a temperatura de la sala, seguidos por la adición de 1-fenilmetanosulfonamida (221 mg, 1.30 mmol). La mezcla de reacción se agitó de un día para otro, luego de lo cual se agregaron una cantidad adicional de TBTU (14mg, 0.044 mmol) y 1-fenilmetanosulfonamida (8 mg, 0.047 mmol). La mezcla de reacción se agitó entonces durante otras 3 horas antes de diluirla con DCM y se lavó dos veces con 1% KHSO4 (acuoso) x2. La fase acuosa se extrajo con dos veces con DCM y las fases orgánicas combinadas se pasaron a través de un separador de fase y se siguieron por el retiro de disolventes *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8, 55 x 300mm), con el fin de evitar la precipitación del compuesto, el cual se cargó en la columna usando 5% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7. El producto se eluyó empleando una gradiente de 30-100% acetonitrilo/ amortiguador NH_4OAc acuoso, pH 3. Las fracciones que contenían el producto se concentraron *in vacuo*, se disolvieron en acetato de etilo y se lavaron con salmuera. La fase acuosa se extrajo dos veces con acetato de etilo y las fases orgánicas combinadas se concentraron *in vacuo* para producir etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-metilnicotinato como un sólido blanco/amarillo. Rendimiento = 267 mg (51%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 1.74 - 1.59 (2H, m), 1.84 - 1.74 (2H, m), 2.49 (1H,s), 2.60 (3H, s), 2.86 (2H, t, J = 12.7 Hz), 4.10 - 4.00 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.67 (2H, s), 7.44 - 7.23 (5H, m), 8.03 (1H, s), 11.57 (1H, s). MS $^m/_z$: 480(M+1).

Ejemplo 132

4-Fluorobencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

a) 4-Fluorobencil 6-cloro-5-ciano-2-metilnicotinato

Etil 5,6-dicloro-2-metilnicotinato (120, 0.56 mmol) se disolvió en THF seco (4mL), y se agregaron DIPEA (0.2mL, 1.15 mmol) y (4-fluorofenil)metanol (0.062 mL, 0.57 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 15 horas. Los disolventes se retiraron *in vacuo* y el producto crudo se utilizó en el siguiente paso sin purificación.

b) 4-Fluorobencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

El 4-fluorobencil 6-cloro-5-ciano-2-metilnicotinato crudo (137 mg, 0.47 mmol) se disolvió en THF (2mL), MeOH(2mL), y se agregaron DIPEA (0.1mL) y *N*-(bencilsulfonil)piperidin-4-carboxamida (140 mg, 0.49mmol). La mezcla de reacción se calentó a 120°C durante 5 minutos usando calentamiento de microondas de nodo simple. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo tres veces con DCM. La capa orgánica combinada se pasó por un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8 10um, 21.5 x 250 mm) empleando una gradiente de 30-55% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7, para producir 4-fluorobencil 6-(4-{[bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato. Rendimiento = 39 mg (16%).

^{1}H NMR (500MHz, DMSO-d_6) δ 1.64 (2H, m), 1.84 (2H, m), 2.58 (1H, m), 2.65 (3H, s), 3.15 (2H, m), 4.54 (2H, m), 4.69 (2H, s), 5.27 (2H, s), 7.23 (2H, m), 7.29 (2H, m), 7.40 (3H, m), 7.54 (2H, m), 8.38 (1H, s), 11.61 (1H, s). LCMS$^+$/$_Z$: 551.2 (M+1), 549.3 (M-1).

Ejemplo 133

Etil 5-ciano-6-[4-({[(4-etilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (95 mg, 0.30 mmol) se disolvió en DCM (1mL) y se agregaron HATU (148 mg, 0.39 mmol), seguido por DIPEA (155 mg, 1.20mmol). La mezcla se agitó a temperatura de la sala durante 5 minutos antes de la adición de 1-(4-etilfenil)metanosulfonamida (66 mg, 0.33 mmol), elaborada del cloruro de sulfonilo correspondiente en una manera similar al Ejemplo 65b. La mezcla de reacción se agitó durante 18 horas, seguida por la adición de 1-(4-1-(4-etilfenil)metanosulfonamida (10 mg, 0.05 mmol) en 0.2 mL DCM, seguido por HATU (20 mg, 0.053 mmol) y se continuó la agitación a temperatura de la sala durante 22 horas. Los disolventes se retiraron *in vacuo* y el material crudo se disolvió en DMSO (10 mL) y se purificó mediante HPLC de fase inversa preparativa. Disolventes empleados: A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal=20 mL/minuto. Incrementado a un caudal = 100 mL/minuto, 3 minutos después de la inyección. Luego se cambió a A/B/C 5:0:95. Incrementado a 100:0:0 durante 20 minutos, en 9 pasos iguales. Columna: Kromasil C8, 250 mm x 50.8 ID. Las fracciones relevantes se concentraron y se secaron por congelamiento de un día para otro para producir 0.071 g del compuesto del título. La sal de Na se elaboró suspendiendo el material en acetonitrilo (0.4 mL) y agregando 1.0 equivalentes 0.1 M NaOH (1.42 mL) y algo de agua (aprox. 10 mL). Después de agitar durante 5 minutos, casi todo el material se había transformado en una solución. Los sólidos se retiraron mediante filtración y la fase de la solución se secó por congelamiento. Esto produjo etil 5-ciano-6-[4-({[(4-etilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato. Rendimiento = 0.076 g (49%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17 (3H, t, J = 7.6 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.54-1.67 (2H, m), 1.76-1.85 (2H, m), 2.20-2.30 (1H, m), 2.56 (2H, q, J = 7.6 Hz), 2.65 (3H, s), 3.17- 3.27 (2H, m), 4.20 (2H, s), 4.26 (2H, q, J = 7.1 Hz), 4.39-4.47 (2H, m), 7.09 (2H, br d, J = 8.1 Hz), 7.15 (2H, br d, J = 8.1 Hz), 8.32 (1H, s). MS $^m/_z$: 499 (M+1).

Ejemplo 134

Preparado de acuerdo con el método B a partir de 1-(3,4-difluorofenil) metanosulfonamida, elaborada del cloruro de sulfonilo correspondiente en una forma similar al Ejemplo 65b. Rendimiento = 4 mg (4%).
MS $^{m}/_{z}$: 479 (M+1).

Ejemplo 135

Etil 5-ciano-6-[4-({[(4-metoxibencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (40 mg. 0.126 mmol) se disolvió en 0.5 mL DCM y se agregaron TBTU (57 mg, 0.18 mmol) y DIPEA (0.064mL, 0.38 mmol). La solución se agitó a temperatura de la sala durante 5 minutos, seguida por la adición a 1-(4-metoxifenil)metanosulfonamida (32 mg, 0.16 mmol), la cual se preparó del cloruro correspondiente en una forma similar al Ejemplo 109, en DCM. La mezcla de reacción se agitó durante 2.5 días, seguida por purificación mediante HPLC de fase inversa. Disolventes empleados: A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 10 mL/minuto. Incrementado a un caudal = 20 mL/minuto justo después de la inyección. Luego cambió a A/B/C 5:0:95. Se incrementó a 50:0:50 durante 30 minutos en 9 pasos iguales. Luego a 100:0:0 durante 10 minutos, en 5 pasos. Caudal: 20 mL/minuto. Columna: Kromasil C8, 250 mm x 20 ID. El material se adhirió a la columna y no se eluyó hasta que A/B/C fue de 95/0/5 a 100/0/0.

Para las fracciones relevantes, los disolventes orgánicos se retiraron *in vacuo*, seguidos por secamiento por congelamiento. Se agregó 1 equivalente de 0.1 M NaOH. El material se secó nuevamente por congelamiento para producir etil 5-ciano-6-[4-({[(4-metoxibencil) sulfonil]

amino}carbonil)piperidin-1-il]-2-metilnicotinato. Rendimiento = 34 mg (45%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, d, *J* = 7.1 Hz, 1.55-1.68 (2H, m), 1.77-1.86 (2H, m), 2.27-2.36 (1H, m), 2.66 (3H, s), 3.16-3.25 (2H, m), 3.74 (3H, s), 4.22-4.30 (4H, m), 4.42- 4.51 (2H, m), 6.85 (2H, br d, *J* = 8.5 Hz), 7.16 (2H, br d, *J* = 8.5 Hz), 8.33 (1H, s). MS $^m/_z$: 523 (M+ 1).

Ejemplo 136

Etil 5-ciano-2-metil-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato

Ácido l-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico (143mg, 0.45 mmol) se disolvió en DCM seco (4mL), se agregaron TBTU (168 mg, 0.52 mmol)) y DIPEA(0.16ml, 0.92 mmol). La mezcla se agitó a temperatura de la sala durante 30 minutos y se agregó 1-(3-metilfenil)metanosulfonamida (103 mg, 0.56 mmol). La mezcla de reacción se agitó a temperatura de la sala durante 22 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo tres veces con DCM. La capa orgánica combinada se pasó por un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8 10μm, 21.5 x 250mm) empleando una gradiente de 25-45% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7, para producir etil 5-ciano-2-metil-6-[4-({[(3-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato. Rendimiento = 160 mg (73%).

^{1}H NMR (500MHz, DMSO-d_6): δ 1.31 (3H, t, *J* =7.0), 1.64 (2H, m), 1.82 (2H, m), 2.31 (3H, s), 2.59 (1H, m), 2.65 (3H, s), 3.14 (2H, m), 4.26 (2H, q, *J* = 7.0), 4.54 (2H, m), 4.65 (2H, s), 7.10 (2H, m), 7.21 (1H, m), 7.29 (1H, m), 8.35 (1H, s), 11.58 (1H, s). MS$^m/_z$: 485.2 (M^{+1}), 483.2 (M^{-1}).

Ejemplo 137

Etil 5-ciano-6-[3-({[(4-etilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (145 mg, 0.500 mmol) se disolvió en 2 mL DCM/DMF 1:1 y TBTU (265 mg, 0.700 mmol), DIPEA (0.34 mL, 2 mmol) y 1 mL DMF. La mezcla se agitó a temperatura de la sala durante 5 minutos antes de la adición de 1-(4-etilfenil)metanosulfonamida (120 mg, 0.600mmol), elaborada del cloruro de sulfonilo correspondiente en una forma similar al Ejemplo 65b, en 1 mL DCM. La mezcla de reacción se agitó durante el fin de semana, seguida por la adición de más 1-(4-etilfenil)metanosulfonamida (10 mg, 0.05 mmol) en 0.2 mL DCM, seguido por TBTU adicional (20 mg, 0.05 mmol) y se continuó la agitación a temperatura de la sala durante 22 horas más. Los disolventes se retiraron *in vacuo*, seguidos por la adición de DMSO (10 mL). La purificación se llevó a cabo mediante HPLC de fase inversa. Disolventes empleados: A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 20 mL/minuto. Incrementado a un caudal = 100 mL/minuto, 3 minutos después de la inyección. Luego cambió a A/B/C 5:0:95. Tuvo que reducirse el caudal a 50 mL/minuto (caudal = 100 mL/minuto produjo separación automática debida al aumento de la presión interna). Se incrementó a 50:0:50 durante 15 minutos en 5 pasos. Luego a 100:0:0 durante 15 minutos en 5 pasos. Columna: Kromasil C8, 250 mmx50.8 ID. La fracción relevante se concentró *in vacuo* y se secó por congelamiento de un día para otro. Esto proporcionó 0.111 g de producto. La sal Na se elaboró suspendiendo el material en acetonitrilo (1 mL) y agregando 1.0 equivalente 0.1 M NaOH (2.36 mL) y algo de agua (aprox. 10 mL). Después de agitar durante 5 minutos, casi todo el material se había convertido en una solución. Los sólidos se retiraron por filtración (jeringa + filtro) y el líquido se secó por congelamiento. Esto produjo etil 5-ciano-6-[3-({[(4-etilbencil)sulfonil] amino}carbonil)azetidin-1-il]-2-metilnicotinato. Rendimiento = 120 mg (49%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.16 (3H, t, J = 7.6 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.55 (2H, q, J = 7.6 Hz), 2.64 (3H, s), 3.15-3.25 (1H, m), 4.22-4.27

(4H, m), 4.27-4.40 (4H, m), 7.05 (2H, br d, J = 8.0 Hz), 7.15 (2H, br d, J = 8.0 Hz), 8.28 (1H, s). MS $^{m}/_{z}$: 471 (M+1).

Ejemplo 138

Etil 5-cloro-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino} carbonil) azetidin-1-il]nicotinato

Una solución de ácido 1-[3-cloro-5-(etoxicarbonil)-6-metilpiridin-2-il] azetidin-3-carboxílico (235 mg, 0.788 mmol), DIPEA (686µl, 3.94 mmol) y TBTU (303mg, 0.945 mmol) en DCM seco (5mL) se agitó durante 10 minutos a temperatura de la sala, seguidos por la adición una solución de 1-(4-metilfenil) metanosulfonamida (175 mg, 0.945 mmol) en DCM seco (1mL). La mezcla de reacción se agitó de un día para otro seguida por la adición de 2% KHSO4 (acuoso), las fases se separaron y la fase orgánica se lavó con 2% KHSO4 (acuoso). La fase acuosa se extrajo dos veces con DCM y las fases orgánicas combinadas se filtraron a través de un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8, 50.8 x 300 mm); con el fin de evitar la precipitación, el compuesto se cargó en la columna usando 5% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7. El producto se eluyó empleando una gradiente de 5-90% acetonitrilo/ amortiguador NH_4OAc acuoso, pH 3, para producir etil 5-cloro-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato como un sólido blanco luego del secamiento por congelamiento. Rendimiento = 289 mg (78%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.4 Hz), 2.28 (3H, s), 2.59 (3H, s,), 3.41- 3.53 (1H, m), 4.16-4.29 (4H, m), 4.29-4.39 (2H, m), 4.67 (2H, s), 7.11-7.25 (4H, m), 7.93 (1H, s), 11.71 (1H, s). MS $^{m}/_{z}$: 466 (M+1).

Ejemplo 139

Etil 5-ciano-6-[4-({[(3,4-difluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato

Preparado de acuerdo con el método B a partir de 1-(3,4-difluorofenil) metanosulfonamida, elaborada del cloruro de sulfonilo correspondiente en una forma similar al Ejemplo 65b. Rendimiento = 16 mg (16%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.53 - 1.70 (2H, m), 1.76 - 1.90 (2H, m), 2.47 - 2.54 (1H, m), 2.64 (3H, s), 3.15 (2H, app. t, J = 11.6 Hz), 4.25 (2H, q, J = 7.1 Hz), 4.47 - 4.57 (2H, m), 4.67 (2H, s), 7.08 - 7.18 (1H, m), 7.30 - 7.40 (1H, m), 7.41 - 7.53 (1H, m), 8.34 (1H, s), 11.42 - 12.03 (1H, m). MS $^m/_z$: 507 (M+1).

Ejemplo 140

Etil 5-ciano-6-[3-({[(4-metoxibencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato

Ácido 1-[3-ciano-5-(etoxicarbonil)-6-metilpiridin-2-il]azetidin-3-carboxílico (43 mg, 0.150 mmol) se disolvió en 0.5 mL DCM, seguido por la adición de TBTU (67 mg,0.21 mmol) y DIPEA (0.076 mL, 0.45 mmol). La solución se agitó a temperatura de la sala durante 5 minutos, seguida por la adición 1-(4-metoxifenil)metanosulfonamida (80 mg, 0.180 mmol), la cual se preparó del cloruro correspondiente en una forma similar al Ejemplo 109, disuelta en DCM. La mezcla de reacción se agitó durante 18 horas, seguida por la adición de TBTU(34 mg, 0.11 mmol) y DIPEA (0.152mL, 0.89 mmol). La mezcla de reacción se agitó durante 5 minutos, seguida por la adición de 1-(4-metoxifenil)metanosulfonamida (27 mg, 0.060 mmol, 45%), se disolvió en 0.2 mL DMF y se agregó a la mezcla de reacción. Se continuó la agitación a temperatura de la sala durante 16 horas. Los disolventes se retiraron *in vacuo* y el material crudo se disolvió en 5 mL de acetato de etilo, seguido por la extracción con 2x5mL 1M NaHSO4 y 1x5 mL salmuera. La capa orgánica se aisló, se secó sobre sulfato de sodio, se filtró y los disolventes se retiraron *in vacuo* para producir 0.136 g de material crudo. La purificación se llevó a cabo mediante HPLC de fase

inversa. Disolventes empleados: A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 10 mL/minuto. Incrementado a un caudal=20 mL/ minuto justo después de la inyección. Luego cambió a A/B/C 5:0:95. Se incrementó a 50:0:50 durante 30 minutos en 9 pasos iguales. Luego a 100:0:0 durante 10 minutos en 5 pasos. Caudal: 20 mL/minuto. Columna: Kromasil C8, 250 mmx20 ID. El material se adhirió a la columna y no se eluyó hasta que A/B/C fue de 95/0/5 a 100/0/0. La fracción relevante se evaporó y se secó por congelamiento, se cuantificó (0.032 g) y se agregó 1 equivalente 0.1 M NaOH. El material se secó por congelamiento para producir etil 5-ciano-6-[3-({[(4-metoxibencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato.
Rendimiento = 34 mg (48%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.2 Hz), 2.63 (3H, s), 3.14-3.23 (1H, m), 3.72 (3H, s), 4.21 (2H, s), 4.25 (2H, q, J = 7.2 Hz), 4.28-4.39 (4H, m), 6.79 (2H, br d, J = 8.6 Hz), 7.16 (2H, br d, J = 8.6 Hz), 8.28 (1H, s). MS $^m/_z$: 473 (M+1).

Ejemplo 141

Ciclopropil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Ácido 1-{3-ciano-5-[(ciclopropiloxi)carbonil]-6-metilpiridin-2-il}piperidin-4-carboxílico (40 mg, 0.12 mmol) se disolvió en DCM, seguido por la adición de TBTU (46.8 mg , 0.15 mmol) y DIPEA (0.11 mL, 0.61 mmol) después de 10 minutos. La mezcla de reacción se agregó a 1-(4-metilfenil) metanosulfonamida (27 mg, 0.15 mmol) y se agitó de un día para otro. Los disolventes se retiraron *in vacuo* y el material crudo se repartió en porciones entre EtOAc (5ml)/l MKHSO4 (1mL). La capa orgánica se lavó con agua (1mL) y los disolventes se retiraron *in vacuo*. El compuesto se purificó mediante HPLC preparativa para producir ciclopropil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato como un sólido blanco. Rendimiento = 1 1 mg (97%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.71 - 0.85 (4H, m), 1.56 - 1.70 (2H, m), 1.78 - 1.90 (2H, m), 2.31 (3H, s), 2.55-2.62 (1H, m), 2.63 (3H, s), 3.07 - 3.20 (2H, m), 4.23 - 4.28 (1H, m), 4.48 - 4.60 (2H, m), 4.64 (2H, s), 7.17 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz), 8.30 (1H, s), 11.55 (1H, S). MS $^m/_z$: 497(M+1).

Ejemplo 142

Etil 5-ciano-2-metil-6-[3-({[(piridin-4-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato

Preparado de acuerdo con el método B a partir de 1-piridin-4-ilmetanosulfonamida, la cual se preparó del bromuro correspondiente en una forma similar al Ejemplo 109, paso a). Rendimiento = 7 mg (8%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 6.9 Hz), 2.63 (3H, s), 3.39 - 3.49 (1H, m), 4.21 - 4.26 (2H, m), 4.28 - 4.55 (4H, m), 4.64 (2H, s), 7.28 - 7.42 (2H, m), 8.30 (1H, s), 8.48 - 8.62 (2H, m). MS $^m/_z$: 444 (M+1).

Ejemplo 143

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(dimetilamino)nicotinato

a) Ácido 1-[3-ciano-6-(dimetilamino)-5-(etoxicarbonil)piridin-2-il] azetidin-3-carboxílico

Etil 6-cloro-5-ciano-2-(dimetilamino)nicotinato (507 mg, 1.60 mmol) se disolvió en etanol/agua 1:1, seguido por la adición de ácido azetidin-3-carboxílico (242 mg, 2.39 mmol) y TEA (0.644 mL, 4.80 mmol). La mezcla de reacción se calentó en un horno microondas, calentamiento de nodo simple, a 120°C durante 20 minutos. Los disolventes se retiraron *in vacuo* y el residuo se disolvió en 15 mL DMSO. Se retiró alguna parte de material no disuelto mediante filtración antes de la purificación mediante HPLC de fase inversa.
A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50 mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado

a un caudal = 10 mL/minuto. Incrementado a un caudal = 50 mL/minuto, continuo durante 3 minutos después de la inyección. Luego cambió a A/B/C 5:0:95 y el caudal se incrementó a 100 mL/minuto. Se incrementó a 100:0:0 durante 17 minutos en pasos de puntos de 5%. Columna: Kromasil C8, 250 mmx50.8 ID.

Esto produjo ácido 1-[3-ciano-6-(dimetilamino)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico. Rendimiento = 0.064 g.(13%).

b) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(dimetilamino)nicotinato

Ácido 1-[3-ciano-6-(dimetilamino)-5-(etoxicarbonil)piridin-2-il]azetidin-3 - carboxílico (64 mg, 0.200 mmol) se disolvió en DCM y se agregaron TBTU (96 mg, 0.300 mmol) y DIPEA (0.136 mL, 0.800mmol). La mezcla se agitó durante 5 minutos a temperatura de la sala antes de la adición de 1-fenilmetanosulfonamida (48 mg, 0.28 mol). La mezcla de reacción se agitó a temperatura de la sala, durante 16 horas. Se agregaron 1-fenilmetanosulfonamida (48 mg, 0.28 mol), TBTU (96 mg, 0.300 mmol) y DIPEA (0.136 mL, 0.800mmol) y la agitación a temperatura de la sala se continuó durante 20 horas más. Se agregó hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (93 mg, 0.20 mmol) y la mezcla se agitó a temperatura de la sala durante 3.5 días (optimizada-no optimizada). Se agregó cloruro de tionilo (0.044 mL, 0.600 mmol) y la mezcla de reacción se agitó durante 16 horas más. La purificación se efectuó mediante HPLC de fase inversa. A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5. Inicio: A/B 5:95. Inyectado a un caudal = 10 mL/minuto. Incrementado a un caudal = 20 mL/minuto, 3 minutos después de la inyección. Luego cambió a A/B/C 5:0:95. Se incrementó a 100:0 durante 20 minutos, aumentando con el mismo intervalo cada minuto. Caudal: 20 mL/minuto. Columna: Kromasil C8, 250 mm x 20 ID. Esto proporcionó un producto que sólo era 71% puro. El resto fue el subproducto guanidina.

La re-purificación se efectuó mediante HPLC de fase inversa. A: MeCN, B: 0.1 M acetato de amonio/MeCN 95:5, C: 5% MeCN en 50 mM HCOOH/50

mM formiato de amonio. Inicio: A/B/C 5:95:0. Inyectado a un caudal = 10 mL/minuto. Incrementado a un caudal = 20 mL/minuto, 3 minutos después de la inyección. Luego cambió a A/B/C 5:0:95. Se incrementó a 100:0:0 durante 20 minutos en pasos iguales. Caudal: 20 mL/minutos. Columna: Kromasil C8, 250 mmx20 ED.

El método anterior produjo etil 6-(3-{[(bencilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-(dimetilamino)nicotinato. Rendimiento: 11 mg (12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.40 (3H, m), 3.03 (6H, s), 3.00-3.06 (2H, m), 4.21- 4.40 (5H, m), 4.67 (2H, s), 7.33-7.45 (5H, m), 8.10 (1H, s). MS $^m/_z$: 472 (M+1).

Ejemplo 144

1-Óxido de etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

a) 1-Óxido de etil 6-cloro-5-ciano-2-metilnicotinato

Etil 6-cloro-5-ciano-2-metilnicotinato (1.00 g, 4.45 mmol) se disolvió en DCM (25mL) y se enfrió en un baño de hielo. Peróxido de hidrógeno de urea (2.09 g, 22.3 mmol) se cargó y se agregó anhídrido de ácido trifluoroacético (3.11 mL, 22.3 mmol) gota a gota durante 2-3 minutos. El baño se enfriamiento se retiró después de 15 minutos y la mezcla de reacción se agitó de un día para otro. Se agregó pirosulfito de sodio (4.2 g en 15 mL de agua) y la mezcla de reacción se agitó durante 3 minutos, seguida por la adición de DCM (5ml) y 1M KHSO4 (2ml) y se continuó la agitación durante 5 minutos. La capa acuosa se extrajo tres veces con DCM y los orgánicos combinados se secaron sobre sulfato de sodio. La concentración suministró 900mg de un sólido pegajoso amarillo claro. El material crudo se purificó mediante HPLC preparativa, 50x300mm, C8, 10um para producir 1-óxido de etil 6-cloro-5-ciano-2-metilnicotinato. Rendimiento = 356mg (33%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.34 (3H, t, J = 7.1 Hz), 2.68 (3H, s), 4.36 (2H, q, J =7.1 Hz), 8.25 (1H, s).

b) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

1-Óxido de etil 6-cloro-5-ciano-2-metilnicotinato (50 mg, 0.21 mmol) y *N*-(bencilsulfonil)piperidin-4-carboxamida (59 mg, 0.21 mmol) se cargaron en un matraz y se disolvieron en EtOH (2mL), luego de lo cual se agregó DIPEA (0.072 mL, 0.42 mmol). La mezcla de reacción se concentró *in vacuo* después de 10 minutos. El producto crudo se purificó usando HPLC preparativa para producir 1-oxido de etil 6-(4-{[bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato. Rendimiento = 65mg: (64%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (3H, 1, *J* =7.1Hz), 1.70-1.84 (4H, m), 2.04-2.25(1H, m), 2.63(3H, s), 3.16-3.25(2H, m), 3.54(1H, br s), 3.71-3.80(2H, m), 4.26(2H, s), 4.30(2H, q, *J* =7.1), 7.21-7.30 (5H, m), 7.95 (1H, s). MS $^m/_z$: 487(M+1).

Ejemplo 145

Etil 5-acetil-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-2-metilnicotinato

a) Etil 5-acetil-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato

3-Oxobutanamida (54.5 g, 539 mmol) se suspendió en 400 mL EtOH. Se agregó gota a gota NaOEt/EtOH (210mL, 564 mmol, 21%) y la mezcla de reacción se agitó a temperatura de la sala durante 1 hora. Se agregó gota a gota etil (2*E*)-2-acetil-3-(dimetilamino)acrilato (100g, 513 mmol), disuelto en 400 mL EtOH, y la mezcla de reacción se agitó de un día para otro. La mezcla de reacción se concentró *in vacuo* y el residuo se disolvió en agua y se acidificó a pH 1 con HCl concentrado. La reacción se agitó durante 2 horas, seguida por ajuste del pH a ~ 8 usando carbonato de potasio sólido y bicarbonato de sodio saturado. La mezcla de reacción se extrajo en EtOAc, y DCM, y cada uno de los orgánicos se lavó con salmuera. Los orgánicos combinados se secaron sobre MgSO4, se pasaron por un tapón de sílice. Los disolventes se retiraron *in vacuo* y los sólidos restantes se trituraron

usando 400 mL éter/hexano (1:1). Esto produjo etil 5-acetil-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido.

b) Etil 5-acetil-6-cloro-2-metilnicotinato

Etil 5-acetil-2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (1.67g, 7.48 mmol) se disolvió en $POCl_3$ (13mL, 139 mmol) y la mezcla se calentó a 110°C y se hizo refluir de un día para otro. Se disminuyó la temperatura a la temperatura de la sala, seguida por el retiro de $POCl_3$ bajo presión reducida. El producto crudo se disolvió en DCM, se lavó dos veces con $NaHCO_3$ saturado, seguido por salmuera y agua. La fase acuosa se extrajo con DCM y las fases orgánicas se combinaron y los disolventes se retiraron *in vacuo*. El material crudo se co-concentró de EtOH y DCM una vez cada uno para producir el material crudo etil 5-acetil-6-cloro-2-metilnicotinato, el cual se utilizó inmediatamente en el paso consecutivo.

c) Ácido 1-[3-acetil-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico

Etil 5-acetil-6-cloro-2-metilnicotinato (600mg, 2.11 mmol)) y ácido piperidin-4-carboxílico (299 mg, 2.32 mmol) se disolvieron en agua (4ml) y MeCN (6ml), seguidos por la adición de TEA (1.18mL, 8.44 mmol). La mezcla de reacción se calentó en un horno microondas de nodo simple durante 20 minutos a 120°C. La mezcla de reacción se diluyó con DCM, se lavó con 1%$KHSO_4$ dos veces, las fases acuosas combinadas se extrajeron con DCM y las fases orgánicas combinadas se filtraron a través de un separador de fase y los disolventes se retiraron *in vacuo* para producir ácido 1-[3-acetil-5-(etoxicarbonil)-6-metilpiridin-2-il]piperidin-4-carboxílico como un producto crudo, el cual se utilizó inmediatamente en el siguiente paso. Rendimiento = 2.42 g (114%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63 - 1.47 (2H, m), 1.92 - 1.78 (2H, m), 2.46 (3H, s), 2.61 (3H, s), 3.13 - 2.99 (2H, m), 3.87 - 3.74 (2H, m), 4.24 (2H, q, J = 7.0 Hz), 8.21 (1H, s).

d) Etil 5-acetil-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-2-metilnicotinato

Una solución de ácido 1-[3-acetil-5-(etoxicarbonil)-6-metilpiridin-2-il] piperidin-4-carboxílico (872mg, 2.61 mmol)), DIPEA (2.27mL, 13.0 mmol) y TBTU (1.0 g, 3.11 mmol) en DCM seco (15mL) se agitó durante 15 minutos a temperatura de la sala, seguido por la adición de 1-fenilmetanosulfonamida (536 mg, 3.13 mmol). La mezcla de reacción se agitó de un día para otro, seguida por la adición de TBTU (100 mg, 0.31 mmol) y fenilmetanosulfonamida (53 mg, 0.31 mmol). La mezcla de reacción se agitó entonces durante 5 horas, seguida por la adición de DCM. La mezcla de reacción se lavó dos veces con 1% KHSO4 (acuoso). La fase acuosa se extrajo con DCMx2 y las fases orgánicas combinadas se pasaron a través de un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8, 50.8 x 300 mm). Con el fin de evitar la precipitación, el compuesto se cargó en la columna usando 5% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7. El producto se eluyó empleando una gradiente de 40-10% acetonitrilo/ amortiguador NH_4OAc acuoso, pH 3. Las fracciones que contenían el producto se concentraron *in vacuo*, se disolvieron en DCM y se lavaron con agua. La fase acuosa se extrajo dos veces con DCM y las fases orgánicas combinadas se concentraron *in vacuo* para producir etil 5-acetil-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-2-metilnicotinato como un sólido blanco/amarillo. Rendimiento = 607 mg (48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz), 1.67 -1.85 (4H, m), 2.29-2.40 (1H, m) 2.50 (3H, s), 2.70 (3H, s), 2.94-3.04 (2H, m), 3.91-4.01 (2H, m), 4.32 (2H, q, J = 7.2 Hz), 4.64 (2H, s), 7.27- 7.41 (4H, m), 7.51 (1H, s), 8.38 (1H, s). MS $^m/_z$: 488(M+1).

Ejemplo 146

Etil 6-{4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil) amino]piperidin-1-il}-5-ciano-2-metilnicotinato

a) Bencil 4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil) amino]piperidin-1-carboxilato

Ácido 1-[benciloxi)carbonil]-4-[(*terc*-butoxicarbonil)amino]piperidin-4-carboxílico (468mg, 1.24 mmol)), TBTU (440mg, 1.36 mmol) y DIPEA (0.3mL, 1.72 mmol) se disolvieron en DCM seco (4mL) y se agitaron a temperatura de la sala durante 1 hora. Se agregó 1-fenilmetanosulfonamida (217 mg, 1.27 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 17 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM tres veces. Las capas orgánicas combinadas se corrieron a través de un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó mediante HPLC preparativa, columna: Kromasil C8 10µm, 21.5 x 250 mm, fase móvil A: 100%, fase móvil B: 5% AcN, 95% NH_4AcO (acuoso) (pH 7), gradiente: 20=>40% A durante 35 minutos, caudal: 25ml/min, UV: 220 nm para producir bencil 4-{[(bencilsulfonil) amino]carbonil}-4-[(*terc*-butoxicarbonil)amino]piperidin-1-carboxilato. Rendimiento = 297mg (45%). LCMS: m/z: 530.4 (M-1).

b) *terc*-Butil (4-{[(bencilsulfonil)amino]carbonil}piperidin-4-il) carbamato

Bencil 4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil) amino] piperidin-1-carboxilato (297mg, 0.56 mmol), $Pd(OH)_2$(96mg, 0.136 mmol, 20% en peso) y formiato de amonio (544mg, 8.63 mmol) se suspendieron en MeOH(10mL) en un frasco microondas de 20 mL. La mezcla de reacción se calentó a 120°C durante 5 minutos empleando calentamiento en microondas de nodo simple. Se agregaron $Pd(OH)_2$(50mg, 0.094 mmol, 20% en peso) y formiato de amonio (300mg, 4.76 mmol), y la mezcla de reacción se calentó a 12°C durante 5 minutos. Se agregaron una cantidad adicional de $Pd(OH)_2$ (50mg, 0.094 mmol) y formiato de amonio (400mg, 6.34 mmol), y la mezcla de reacción se calentó a 12°C durante 10 minutos. La mezcla de reacción se filtró y se evaporó. El producto crudo se utilizó en el siguiente paso sin purificación adicional.

LCMS$^{+}/_{2}$: 398.2(M+1), 396.3(M-1).

c) Etil 6-{4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil) amino]piperidin-1-il}-5-ciano-2-metilnicotinato

terc-Butil (4-{[(bencilsulfonil)amino]carbonil}piperidin-4-il)carbamato (107 mg, 0.27 mmol) y etil 6-cloro-5-ciano-2-metilnicotinato (124 mg, 0.55 mmol) se disolvieron en EtOH (7mL) y H_2O (2mL), y se agregó DIPEA (1.3mL, 7.46 mmol). La mezcla de reacción se calentó a 12°C durante 5 minutos usando calentamiento de microondas de nodo simple. Se agregó $NaHCO_3$ (acuoso), y la mezcla se extrajo tres veces con DCM. La capa orgánica combinada se corrió a través de un separador de fase y los disolventes se retiraron *in vacuo*. El producto crudo se purificó mediante HPLC preparativa, columna: Kromasil C8 10µm, 21.5 x 250mm, fase móvil A: 100% AcN, fase móvil B: 5% AcN, 95% (pH7), gradiente: 25=>50% A 35 minutos, caudal: 25ml/minuto.

156UV: 296nm para producir etil 6-{4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil)amino]piperidin-1-il}-5-ciano-2-metilnicotinato.

Rendimiento = 9 mg (3%).

LCMS$^{+}/_{Z}$: 586.4 (M+1), 584.4(M-1).

Ejemplo 147

Etil 6-(4-amino-4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato

Etil 6-{4-{[(bencilsulfonil)amino]carbonil}-4-[(*terc*-butoxicarbonil) amino]piperidin-1-il}-5-ciano-2-metilnicotinato (7.6mg, 0.013 mmol) se disolvió en DCM(5mL) y se agregó TFA (2mL). La mezcla de reacción se agitó a temperatura de la sala durante 1 hora, seguida por el retiro de los disolventes *in vacuo*. El producto se re-disolvió en AcN/H_2O y se secó por congelamiento proporcionando trifluoroacetato de etil 6-(4-amino-4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato.

Rendimiento = 8mg (100%).

LCMS$^{m}/_{z}$: 486.3(M+1), 484.3(M-1).

Otros Ejemplos

Procedimiento Experimental General

Los espectros de masa se registraron en un espectrómetro de mas de trampa de iones LCQ Duo, equipado con una interfaz de electroaspersión (LC-MS) o un sistema LC-MS conformado por un Waters ZQ que empleaba un sistema LC-Agilent 1100 LC. Las mediciones ^{1}H NMR se realizaron en un espectrómetro Varian Mercury VX 400, que operaba con una frecuencia 1H de 400 y espectrómetros Varian UNITY plus 400, 500 y 600, que operaban con frecuencias 1H de 400, 500 y 600 respectivamente. Los cambios químicos se dan en ppm con el disolvente como estándar interno. Los protones en heteroátomos tales como NH y los protones OH se relacionan únicamente cuando se detectaron en NMR y, en consecuencia, pueden estar ausentes. La cromatografía se realizó empleando gel de sílice Biotage 40S, 40M, 12i o gel de sílice Merck 60 (0.063-0.200 mm). Cromatografía instantánea se realizó usando columnas estándar de vidrio o plástico o en un sistema Biotage Horizon. Las separaciones HPLC se llevaron a cabo en sistemas Waters YMC-ODS AQS-3 120 Angstrom 3 x 500 mm o en uno Waters Delta Prep usando columnas Kromasil C8, 10 µm.

El sistema de purificación y el sistema LC-MS empleados en el Método A' a E' a continuación fue el sistema de purificación Waters Fraction Lynx II: Columna: Sunfire Prep C18, 5 µm OBD, columna 19 x 100 mm. Gradiente 5-95% CH_3CN en 0.1 mM HCOOH (pH=3). Se utilizó recolección de fracciones desencadenada por MS. Se registraron los espectros de masa en un Micromass ZQ single quadropole o un Micromass quattro micro, los dos equipados con una interfaz de electroaspersión, asistida neumáticamente.

Las reacciones se realizaron en un reactor microondas en un Personal Chemistry Smith Creator, Smith synthesizer o un Emrys Optimizer.

Listado de abreviaturas:

Abreviatura	Explicación
AcOH	Ácido acético
aq	Acuoso
br	Amplio
Salmuera	Una solución saturada de cloruro de sodio en agua
BSA	Albúmina sérica bovina
$(BoC)_2O$	di-*terc*-butil dicarbonato
BuLi	Butil litio
CDI	Carbonildiimidazol
d	Doblete
DBU	1,8-Diazabiciclo[5.4.0]undec-7-eno
DCM	Diclorometano
DDQ	2,3-Dicloro-5,6-diciano-1,4-benzoquinona
DIPEA	N,N-Diisopropiletilamina
DMA	N,N-Dimetilacetamida
DMF	N,N-dimetilformamida
DMSO	Sulfóxido de dimetilo
EDCI	Clorhidrato de N-[3-(dimetilamino)propil]-N'-etilcarbodiimida
EtOAc	Acetato de etilo
EtOH	Etanol
HEPES	Ácido [4-(2-hidroxietil)-1-piperazinetanosulfónico
HFA	Hidrofluoroalcanos
HOAc	Ácido acético
HOBT	1-Hidroxibenzotriazol
HPLC	Cromatografía líquida de alta resolución
Hz	Hertz
J	Constante de acoplamiento

LDA	Diisopropilamida de litio
m	Multiplete
Me	Metilo
MHz	Megahertz
mL	Mililitro
MS	Espectros de masa
NCS	N-clorosuccinimida
OAc	Acetato
^{i}PrOAc	Iso-propilacetato
q	Quartete
r.t	Temperatura de la sala
S	Singlete t triplete
TB	Amortiguador Tyrodes
TBME	*terc*-butilmetil éter
TBTU	Tetrafluoroborato de N-[(1H-1,2,3-benzotriazol-1-iloxi) (dimetilamino)metilen]-N-metilmetanaminio
TEA	Trietilamina
Tf	Trifluorometilsulfonilo
TFA	Ácido trifluoroacético
THF	Tetrahidrofurano
TMEDA	N,N,N',N'-tetrametiletilendiamina
Ts	p-toluenosulfonilo

Síntesis de sulfonamidas

La síntesis de las sulfonamidas utilizadas en los siguientes Ejemplos se hizo con uno de los tres métodos descritos más adelante:

i) Haciendo reaccionar el cloruro de sulfonilo correspondiente con amoníaco en THF o MeOH, o mediante tratamiento con hidróxido de

amonio en cloruro de metileno. Las sulfonamidas obtenidas se utilizaron sin purificación adicional.

ii) Siguiendo esencialmente el procedimiento descrito por Seto, T. et. al., en J. Organic Chemistry, vol. 68, No. 10 (2003), páginas 4123-4125.

o

iii) Siguiendo esencialmente el procedimiento descrito por Wang, Z et. al., en Tetrahedron Letters, vol. 43 (2002), páginas 8479-8483.

Síntesis de los Ejemplos

Los siguientes procedimientos generales (es decir, Método A' a E') se utilizaron para preparar algunos de los Ejemplos que siguen y se mencionan en cada Ejemplo específico.

Método A': ejemplificado por el procedimiento del Ejemplo 10

DIPEA (64 mg, 0.5 mmol) se agregó a una solución de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico (35.3 mg, 0.1mmol) y TBTU (38.5 mg, 0.12mmol) en DCM (5mL), y la mezcla se agitó durante 30 minutos a temperatura de la sala antes de agregar 1-(2-fluorofenil)metanosulfonamida (23 mg, 0.12mmol) disuelta en DCM (1 mL). La reacción se dejó agitar de un día para otro. LC-MS mostró que quedó material de partida, y se agregaron más TBTU (19 mg, 0.06mmol) y DIPEA (26 mg, 0.2mmol) a la mezcla y la agitación se continuó durante otras 2 horas. La mezcla de reacción se lavó con 1%$KHSO_4$, la fase acuosa se extrajo con DCM (1ml) y las fases orgánicas combinadas se pasaron a través de un separador de fase y se evaporaron en una centrífuga de vacío. El producto crudo obtenido se purificó mediante HPLC (véase Procedimiento Experimental General) para producir etil 5-ciano-2-

(difluorometil)-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato. Rendimiento: 41 mg (78%).

Método B': ejemplificado por el procedimiento del Ejemplo 42

DIPEA (128 mg, 1.0 mmol) se agregó a una solución de ácido {1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]pirrolidin-3-il}acético (74.2 mg, 0.2mmol) y TBTU (77 mg, 0.24 mmol) en DCM (7mL) y la mezcla se agitó durante 30 minutos a temperatura de la sala antes de agregar 1-fenilmetanosulfonamida (41 mg, 0.24 mmol) disuelta en DCM (1 mL), y la reacción se dejó de un día para otro. La mezcla de reacción se lavó con 1% $KHSO_4$, la fase acuosa se extrajo con DCM y las fases orgánicas combinadas se pasaron a través de un separador de fase y se evaporaron en una centrífuga de vacío. El producto crudo obtenido se purificó mediante HPLC (véase Procedimiento Experimental General) para producir etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}pirrolidin-1-il)-5-ciano-2-(trifluorometil) nicotinato. Rendimiento: 88 mg (84%).

Método C': ejemplificado por el procedimiento del Ejemplo 55

DIPEA (43 mg, 0.3 mmol) y TBTU (64 mg, 0.20 mmol) se agregaron a una solución de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il] piperidin-4-carboxílico (74.2 mg, 0.2 mmol) en DMF y la mezcla se agitó durante 2 horas a temperatura de la sala antes de agregarla a 1-(4-fluorofenil) metanosulfonamida (38 mg, 0.22 mmol) disuelta en DMF. La mezcla de reacción se agitó de un día para otro y se pasó a través de una columna de intercambio iónico SCX-2. El producto crudo obtenido se purificó mediante HPLC (véase Procedimiento Experimental General) para producir etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(trifluorometil)nicotinato. Rendimiento: 4.3 mg (4%).

Método D': ejemplificado por el procedimiento del Ejemplo 45

CDI (26 mg, 0.16 mmol) se agregó a una solución de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico (51 mg, 0,15 mmol) (evolución de gas) en CH_3CN y la mezcla se calentó a 50°C durante 2 horas. La mezcla anterior se agregó entonces a una solución de 1-(4-fluorofenil)metanosulfonamida (28 mg, 0.15 mmol) y DBU (23 mg, 0.15 mmol) en CH_3CN y la reacción se agitó a temperatura de la sala de un día para otro. La purificación mediante HPLC (véase Procedimiento Experimental) produjo etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino} carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato.

Método E': ejemplificado por el procedimiento del Ejemplo 75

DIPEA (38 mg, 0.3 mmol) se agregó a una solución de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico (35.3 mg, 0.1mmol) y TBTU (38.5 mg, 0.12 mmol) en DCM (2mL) y la mezcla se agitó durante 10 minutos a temperatura de la sala antes de agregar 1-(2-fluorofenil)metanosulfonamida (19 mg, 0.10mmol). La reacción se dejó agitar de un día para otro. La mezcla de reacción se lavó con 1M $KHSO_4$ y las fases orgánicas se pasaron a través de un separador de fase y se evaporaron en una centrífuga de vacío. El producto crudo obtenido se purificó mediante HPLC (véase Procedimiento Experimental General) para producir etil 5-ciano- 6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 13 mg (25%).

Ejemplo 148

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-(difluorometil)nicotinato

(a) Etil 2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato

Etil 2-metil-6-oxo-1,6-dihidropiridin-3-carboxilato (2.0 g, 11.04 mmol) (Sobczak, A et al., Synth. Commun, vol. 35, No. 23, 2005, páginas 2993-

3001) se agregó a una solución de 2-metoxi-N-(2-metoxietil)-N-(trifluoro-λ^4-sulfanil)etanamina (7.82 g, 22.08 mmol) en CH_3CN bajo una atmósfera de nitrógeno. La reacción se hizo refluir de un día para otro, luego de lo cual se agregó más 2-metoxi-N-(2-metoxietil)-N-(trifluoro-λ^4-sulfanil)etanamina (2.73 g, 7.7 mmol) y la agitación se continuó hasta que se consumió todo el material de partida. La reacción se diluyó con éter dietílico, se filtró para retirar los sólidos negros, se lavó con agua y $NaHCO_3$ (acuoso, saturado). Las dos fases se filtraron nuevamente para retirar más sólidos negros. La fase acuosa se extrajo con éter dietílico (2 veces) y la fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró y suspendió en éter dietílico para retirar las impurezas amarillas. El secamiento del sólido blanco restante produjo etil 2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato. Rendimiento: 370 mg (14%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J =7.2 Hz), 4.36 (2H, q, J = 7.2 Hz), 6.69 (1H, d, J = 10 Hz), 7.56 (1H, t, J = 54 Hz), 7.99 81H, d, J = 10 Hz).

(b) Etil 5-cloro-2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato
NCS (270 mg, 2.02 mmol) disuelto en DMF (2 mL) se agregó a una solución de etil 2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato (365 mg, 1.44 mmol) y la reacción se calentó a 100 °C de un día para otro. Puesto que aún quedaba material de partida, se agregaron alícuotas adicionales de NCS (135 mg, 1.01 mmol y 5 horas después 270 mg, 2.02 mmol) y se continuó el calentamiento hasta que el material de partida hubo desaparecido. La reacción se diluyó con DCM y se lavó con agua y salmuera. La fase acuosa se extrajo dos veces con DCM y la fase orgánica combinada se pasó a través de un separador de fase y se evaporó. Purificación mediante cromatografía instantánea (Horizon Flash 40+M, Eluyente: se utilizó una gradiente de EtOAc/heptano de 50 a 100% EtOAc)) produjo etil 5-cloro-2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato como un aceite amarillo, el cual se empleó en el siguiente paso sin análisis o purificación posterior. Rendimiento: 88 mg (15%).

(c) Etil 5,6-dicloro-2-(difluorometil)nicotinato

Cloruro de oxalilo (0.1 mL, 1.18 mmol), junto con DMF (0.1 mL), se agregó a una solución de etil 5-cloro-2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato (85.5 mg, 0.217 mmol) en DCM y la mezcla se calentó a 42 °C durante 3 horas. No pudo detectarse ningún producto y, en consecuencia, se agregó otro 0.1 mL (1.18 mmol) de cloruro de oxalilo y la agitación se continuó a 42 °C de un día para otro. La reacción se diluyó con DCM y se extinguió virtiéndola en una mezcla de hielo/agua. Las fases de separaron y la fase orgánica se lavó con $NaHCO_3$ (acuoso, saturado) y salmuera. La fase acuosa combinada se extrajo con DCM y la fase orgánica combinada se filtró a través de un separador de fase y se evaporó. El residuo se co-concentró dos veces con DCM para producir etil 5,6-dicloro-2-(difluorometil)nicotinato como un aceite amarillo, el cual se utilizó en el siguiente paso sin purificación adicional. Rendimiento: 113.5 mg (51%).

(d) *terc*-Butil 4-[(bencilsulfonil)carbamoil]piperidin-1-carboxilato

Trietilamina (591 g, 5840 mmol) se agregó a una suspensión agitada de ácido 1-(*terc*-butoxicarbonil)piperidin-4-carboxílico (448 g, 1954 mmol), LiCl (23.1 g, 545 mmol) y TBTU (657 g, 2046 mmol) en THF (3000 mL) bajo una atmósfera de nitrógeno a temperatura de la sala. Se agregó una solución de 1-fenilmetanosulfonamida (352 g en 1300 mL THF, 2056 mmol) después de 1.5 horas y la agitación se continuó de un día para otro. El disolvente se retiró *in vacuo* para producir una suspensión espesa color café claro/gris (volumen alrededor de 2500 mL). Se agregó EtOAc (3500 mL), seguido por una solución acuosa de HCl (1960 mL 3.6 M HCl y 1960 mL agua). Se retiró la fase acuosa y la fase orgánica se lavó con 2 x 1500 mL 1 M HCl. La fase orgánica se enfrió a 0°C, lo cual produjo un precipitado de HOBt, el cual se extrajo completamente por filtración. La mayor parte del disolvente se retiró *in vacuo* para producir una mezcla café claro-gris espesa. Se agregó EtOH (50%, 4000 mL) y la suspensión se agitó durante 1.5 horas. El producto precipitado se extrajo completamente

por filtración, se lavó con 50% EtOH (500 mL + 2 x 1500 mL) y se secó en un horno de vacío a 25 °C para producir *terc*-butil 4-[(bencilsulfonil)carbamoil]piperidin-1-carboxilato como un sólido blanco. Rendimiento: 584 g (78%).

(e) N-(bencilsulfonil)piperidin-4-carboxamida

terc-Butil 4-[(bencilsulfonil)carbamoil]piperidin-1-carboxilato (583 g, 1524 mmol) se suspendió en ácido fórmico (3000 mL) bajo una atmósfera de nitrógeno y la reacción se agitó durante 20 minutos. La reacción fue espumosa debido a la evolución de gas y se utilizó ácido fórmico (500 mL) para lavar la espuma de las paredes del recipiente de reacción. Después de 2 horas la espumación se había detenido y la reacción era clara con unos pocos sólidos restantes. La reacción se agitó de un día para otro se retiraron *in vacuo* 2500 mL de ácido fórmico. Se agregó agua (1000 mL) y la reacción se filtró. La solución clara se evaporó y se agregó agua (3000 mL). Se utilizó una solución de hidróxido de amonio saturado en agua (en total se agregaron 390 mL y el pH pasó de 3.10 a 6.10) para neutralizar la solución ácida y en el criterio de valoración (pH=6.10) se formó un precipitado pesado del producto. La mezcla se agitó de un día para otro y el precipitado se extrajo completamente por filtración y se lavó con agua (1000 mL). El secamiento en un horno de vacío a 25°C produjo N-(bencilsulfonil)piperidin-4-carboxamida como un polvo blanco. Rendimiento: 372.4 g (87%).

(f) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-(difluorometil)nicotinato

TEA (149 µL, 1.07 mmol) se agregó a una solución de etil 5,6-dicloro-2-(difluorometil)nicotinato (113 mg,0.214 mmol)) y *N*-(bencilsulfonil) piperidin-4-carboxamida (66 mg, 0.24 mmol) en CH_3CN (3 mL) y agua (2 mL). La reacción se calentó en un microondas de nodo simple a 120°C durante 20 minutos. Los disolventes se retiraron *in vacuo* y la mezcla cruda

se diluyó con DCM y se lavó dos veces con 1% $KHSO_4$ (acuoso). Las fases acuosas combinadas se extrajeron con DCM y las fases orgánicas combinadas se pasaron a través de un separador de fase, seguidas por el retiro de los disolventes *in vacuo*. El producto crudo se purificó usando HPLC preparativa en una columna (Kromasil C8, 50.8 x 300 mm), el compuesto se cargó en una columna utilizando 5% acetonitrilo/amortiguador NH_4OAc acuoso, pH 7, y luego se eluyó empleando una gradiente de 30-100% acetonitrilo/ amortiguador NH_4OAc acuoso, pH 3.

Las fracciones de producto se combinaron y el disolvente se retiró *in vacuo*, y se trituró con DCM, seguido por filtración. Los disolventes se retiraron *in vacuo* para producir etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-(difluorometil)nicotinato como un sólido blanco. Rendimiento: 13 mg (11%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (3H, t, J = 7.1 Hz), 1.73-1.91(4H, m), 2.27-2.42 (1H, m), 2.87-3.05 (2H, m), 4.19-4.30 (2H, m), 4.30-4.41(2H, m), 4.67 (2H, s), 7.29 - 7.43 (5H, m), 7.48 - 7.54 (1H, m), 8.16 (1H, s)

Ejemplo 149

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(difluorometil)nicotinato

(a) Etil 5-ciano-2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato

1,1-Dimetoxi-N,N-dimetilmetanamina (4.8 mL, 36.1 mmol) se agregó a etil 4,4-difluoro-3-oxobutanoato (5.0 g, 30.1 mmol) (reacción exotérmica). La solución anaranjada se agitó a temperatura de la sala de un día para otro, se concentró y se co-evaporó con tolueno. El residuo se tomó en EtOH (99.5%, 10 mL) para producir una solución roja. Se agregó NaOEt recién preparado (1M, 30 mL) a una solución de 2-cianoacetamida (2.53 g, 30.1 mmol) en EtOH (99.5%, 30 mL) y la reacción se agitó a temperatura de la sala durante 1 hora y la solución roja ya mencionada se agregó gota a gota.

La suspensión roja formada se agitó de un día para otro y se agregó HOAc (6 mL) y la solución se volvió clara. La solución se concentró y se suspendió en agua (50 mL) y se agitó durante 1 hora, luego de la cual el precipitado se extrajo completamente por filtración y se secó al aire para producir etil 5-ciano-2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido marrón. Rendimiento: 3.03 g (41%).
^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J =7.2 Hz), 4.28 (2H, q, J = 7.2 Hz), 7.48 (1H, t, J = 52.5 Hz, acoplamiento F), 8.58 (1H, s).

(b) Etil 6-cloro-5-ciano-2-(difluorometil)nicotinato

Cloruro de oxalilo (5.3 mL, 62.6 mmol), seguido por DMF (0.097 mL), se agregó a una suspensión de etil 5-ciano-2-(difluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato (3 g, 12.5 mmol) en DCM (45 mL) y la reacción se calentó a 50 °C durante unas cuantas horas, se agregaron más cloruro de oxalilo (1 mL , 11.8 mmol) y DMF (0.2 mL) dos veces con unas pocas horas de intervalo y el calentamiento se continuó a reflujo de un día para otro. La mezcla de reacción se evaporó y el residuo se tomó en DCM y se lavó con agua y $NaHCO_3$ (acuoso, saturado). La fase acuosa se extrajo con DCM (dos veces) y la fase orgánica combinada se concentró se purificó por cromatografía instantánea (Horizon, Eluyente, se utilizó una gradiente de heptano/EtOAc 7/1 a 100% EtOAc) para producir etil 6-cloro-5-ciano-2-(difluorometil)nicotinato como un aceite amarillo. Rendimiento: 2.0 g (60%).
^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.34 (3H, t, J = 7.0), 4.37 (2H, q, J = 7.0 Hz), 7.46 (1H, t, J = 53.2 Hz), 8.99 (1H, s).

(c) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(difluorometil)nicotinato.

TEA (0.4 mL, 2.89 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(difluorometil)nicotinato (200 mg, 0.721 mmol) y N-(bencilsulfonil)piperidin-4-carboxamida (224 mg, 0.793 mmol) en agua (2.5

mL) y EtOH (2 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. Los disolventes se evaporaron y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$ (dos veces). Las fases acuosas combinadas se extrajeron con DCM (dos veces) y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. La purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 40% CH_3CN a 100% CH_3CN/(50 mM HCOOH y 50 mM NH_4OOCH, pH = 3) produjo etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(difluorometil)nicotinato como un sólido blanco. Rendimiento: 250 mg (68%). ^{1}H NMR (400MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.4 Hz), 1.73 - 1.59 (2H, m), 1.91 - 1.81 (2H, m), 2.61 (1H, m), 3.27 - 3.15 (2H, m), 4.28 (2H, q, J = 7.4 Hz), 4.61 - 4.51 (2H, m), 4.69 (2H, s), 7.33 - 7.22 (2H, m), 7.44 - 7.34 (3H, m), 7.53 (1H, s), 8.50 (1H, s), 11.61 (1H, s).

Ejemplo 150

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

(a) Etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato

Cloruro de oxalilo (12.20 g, 96.1 mmol) y DMF (0.744 mL) se agregaron a una solución de etil 5-ciano-6-oxo-2-(trifluorometil)-1,6-dihidropiridin-3-carboxilato (5 g, 19.22 mmol) (preparado esencialmente de acuerdo con el Método D' descrito en Mosti, L et al., Farmaco, vol. 47, No. 4, 1992, páginas 427-437) y la reacción se calentó a 50°C de un día para otro. La reacción se evaporó y el crudo se disolvió en EtOAc y agua. Las fases se separaron y la fase orgánica se lavó con salmuera y $NaHCO_3$ (acuoso, saturado). La fase acuosa se extrajo con EtOAc (3 veces) y la fase orgánica combinada se secó (Na_2CO_3), se filtró y se concentró para producir etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato como un sólido café, el cual se utilizó sin purificación adicional. Rendimiento: 5.206 g (95%).

^{1}H NMR (400 MHz, DMSO-d_6) d 1.31 (t, J = 7.2 Hz, 3H), 4.38 (q, J = 6.9 Hz, 2H), 9.07 (s, 1H)

(b) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

TEA (142 mg, 1.41 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato (140 mg, 0.352 mmol) y N-(bencilsulfonil)piperidin-4-carboxamida (109 mg, 0.387 mmol) en agua (2 mL) y EtOH (2.5 mL).). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. Los disolventes se evaporaron y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$ (dos veces). Las fases acuosas combinadas se extrajeron con DCM (dos veces) y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 30% CH_3CN a 100% CH_3CN/(50 mM HCOOH y 50 mM NH_4OOCH, pH = 3) produjo etil 6-(4-{[(bencilsulfonil)amino]carbonil} piperidin-1-il)-5-ciano-2-(trifluorometil)nicotinato como un sólido blanco. Rendimiento: 107 mg (58%).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.5 Hz), 1.74 - 1.58 (2H, m), 1.91 - 1.79 (2H, m), 2.65-2.54 (1H, m), 3.27 - 3.15 (2H, m), 4.28 (2H, q, J = 7.5 Hz), 4.55-4.46 (2H, m), 4.68 (2H, s), 7.33 - 7.23 (2H, m), 7.47 - 7.35 (3H, m), 8.54 (1H, s), 11.61 (1H, s).

Ejemplo 151

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato

(a) Ácido 1-(*terc*-butoxicarbonil)azetidin-3-carboxílico

$(Boc)_2O$ (25.535 g, 117 mmol) disuelto en MeOH (70 mL) se agregó gota a gota durante 20 minutos a una suspensión agitada de ácido azetidin-3-carboxílico (10.11 g, 100 mmol) y Et_3N (27.8 mL, 200 mmol) en MeOH (105 mL) a temperatura de la sala (reacción moderadamente exotérmica) y la mezcla se agitó de un día para otro (18 horas). La reacción se evaporó a sequedad y se agregó THF (120 mL) y se evaporó para producir ácido 1-

(*terc*-butoxicarbonil)azetidin-3-carboxílico crudo, el cual se utilizó sin purificación adicional en el siguiente paso. Rendimiento: 25.89 g (128%) ^{1}H NMR (400MHz, $CDCl_3$) δ 1.43 (9H, s), 3.21-3.34 (1H, m), 4.00-4.13 (4H, m).

(b) *terc*-Butil 3-[(bencilsulfonil)carbamoil]azetidin-1-carboxilato

TBTU (33.71 g, 105 mmol) y TEA (30.3 g, 300 mmol) se agregaron a una solución de ácido 1-(*terc*-butoxicarbonil)azetidin-3-carboxílico de más arriba (25.89 g, que se asumió que contenía 100 mmol) y la reacción se agitó a temperatura de la sala durante 30 minutos. Se agregaron 1-fenilmetanosulfonamida (17.97 g, 105 mmol) y LiCl (1.844 g, 43.5 mmol) y la agitación se continuó a temperatura de la sala de un día para otro (23 horas). La reacción se concentró a alrededor de 1/3 y se agregó EtOAc (500 mL) y la fase orgánica se lavó con 2 M HCl (1 x 150 mL, 2 x 50 mL), agua (2 x 50 mL). El secamiento ($MgSO_4$), la filtración y la evaporación del disolvente produjeron un polvo color café (48.6 g). El polvo se suspendió en 150 mL TBME y se agitó 3 horas. Los sólidos se extrajeron por filtración y se lavaron con TBME (40 mL). Este procedimiento se repitió dos veces con 100 mL TBME (lavando con 25 mL) para producir un polvo parduzco (33 g) que contenía aún algo de HOBT. El polvo se disolvió en alrededor de 100 mL de EtOH caliente y se agregó agua (130 mL) para inducir una cristalización del producto. Los cristales se extrajeron completamente por filtración y se secaron para producir *terc*-butil 3-[(bencilsulfonil)carbamoil]azetidin-1-carboxilato puro como un polvo blancuzco. Rendimiento: 25.4 g (71%).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.39 (9H, s), 3.30 (1H, m, superpuesto con la señal de agua en DMSO), 3.78-3.95 84H, m), 4.73 (2H, s), 7.28-7.34 (2H, m), 7.36-7.41 (3H, m), 11.71 (1H, br s). MS $^m/_z$: 353 (M-1).

(c) N-(bencilsulfonil)azetidin-3-carboxamida

terc-Butil 3-[(bencilsulfonil)carbamoil]azetidin-1-carboxilato (25.4 g, 71.7 mmol) se agregó a HCOOH (300 mL) a temperatura de la sala y la reacción

se agitó de un día para otro (22 horas). Se retiró el ácido fórmico *in vacuo*, se agregó agua (40 mL) y se retiró *in vacuo*. Se agregó agua (130 mL) al residuo, seguida por NH_4OH (acuoso) hasta que el pH alcanzó 7.4, cuando se inició una cristalización. Los cristales se extrajeron completamente por filtración y se secaron para producir N-(bencilsulfonil)azetidin-3-carboxamida pura como un sólido blanco. Rendimiento: 15.73 g (86%).
^{1}H NMR (400MHz, DMSO-d_6) δ 3.22 (1H, m), 3.87-3.96 (4H, m), 4.28 (2H, s), 7.20-7.32 (5H, m). MS $^m/_z$: 255 (M+1).

(d) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato

TEA (291 mg, 2.88 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(difluorometil)nicotinato (200 mg, 0.721 mmol) y N-(bencilsulfonil)azetidin-3-carboxamida (201 mg, 0.793 mmol) en agua (2 mL) y EtOH (2.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120°C durante 20 minutos. Los disolventes se evaporaron y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$ (dos veces). La fase acuosa combinada se extrajo con DCM (dos veces) y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 40% CH_3CN a 100% CH_3CN/(50 mM HCOOH y 50 mM NH_4OOCH, pH=3) produjo etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato como un sólido blanco. Rendimiento: 264 mg (72%).
^{1}H NMR (400MHz, DMSO-d_6) d 1.30 (3H, t, J = 7.3 Hz), 3.64 - 3.53 (1H, m), 4.27 (2H, q, J = 6.9 Hz), 4.53 - 4.31 (4H, m), 4.75 (2H, s), 7.40 - 7.30 (5H, m), 7.40 (1H, t, J = 53.6 Hz), 8.47 (1H, s), 11.81 (1H, s). MS $^m/_z$: 478 (M+1).

Ejemplo 152

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

(a) Etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato

Cloruro de oxalilo (8.13 mL, 96.1 mmol) y DMF (0.744 mL, 9.61 mmol) se agregaron a una solución de etil 5-ciano-6-oxo-2-(trifluorometil)-1,6-dihidropiridin-3-carboxilato (5.0 g, 19.22 mmol, preparado esencialmente de acuerdo con el procedimiento descrito por Mosti L, et. al., Farmaco, vol. 47, No. 4, 1992, páginas 427-437) y la reacción se calentó a reflujo de un día para otro. El disolvente se evaporó y el residuo se disolvió en EtOAc/agua. Las fases se separaron y la fase orgánica se lavó con salmuera y $NaHCO_3$ (acuoso) (dos veces). La fase acuosa se extrajo con EtOAc (tres veces) y las fases orgánicas combinadas se secaron (Na_2CO_3), se filtraron y se concentraron para producir etil 6-cloro-5-ciano-2-(trifluorometil) nicotinato, el cual se utilizó sin purificación adicional. Rendimiento: 5.21 g (95%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7 Hz), 4.38 (2H, q, J = 7 Hz), 9.07 (1H, s).

(b) Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

TEA (142 mg, 1.41 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato (140 mg, 0.352 mmol) y N-(bencilsulfonil)azetidin-3-carboxamida (98.4 mg, 0.387 mmol) en agua (2 mL) y EtOH (2.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120°C durante 20 minutos. La reacción se filtró para retirar un precipitado y los disolventes se evaporaron. El residuo se tomó en DCM y se lavó con 1% $KHSO_4$ (dos veces). La fase acuosa combinada se extrajo con DCM (dos veces) y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de30% CH_3CN a 100% CH_3CN/(0.1% HCOOH(aq)) produjo etil 6-(3-{[(bencilsulfonil)amino] carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato como un sólido blanco. Rendimiento: 102 mg (58%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.3 Hz), 3.63 - 3.52 (1H, m), 4.27 (2H, q, J = 7.3 Hz), 4.52 - 4.31 (4H, m), 4.74 (2H, s), 8.50 (1H, s), 11.80 (1H, s). MS $^m/_z$: 496 (M+1).

Ejemplo 153

Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(fluorometil)nicotinato

(a) Etil 5-ciano-2-(fluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato

1,1-Dimetoxi-N,N-dimetilmetanamina (4.83 g, 40.5 mmol) se agregó a etil 4-fluoro-3-oxobutanoato (5.0 g, 33.75 mmol) a temperatura de la sala (reacción exotérmica) y la mezcla se agitó de un día para otro, se concentró y se co-evaporó con tolueno. Se agregó EtOH (99.5%, 10 mL) para producir una solución roja. Se agregó una solución 1M de etóxido de sodio (34.5 mL, 2.35 g, 34.5 mmol) a una solución de 2-cianoacetamida (3.12 g, 37.13 mmol) en EtOH (99.5%, 30 mL) y luego de agitar a temperatura de la sala durante 35 minutos, la solución roja ya mencionada se agregó gota a gota y se continuó la agitación de un día para otro. Se agregó cuidadosamente AcOH (6 mL) (reacción exotérmica) y el precipitado formado se filtró y se lavó con éter dietílico. El secamiento proporcionó etil 5-ciano-2-(fluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato como un sólido color crema. Rendimiento: 4.42 g (56%).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.24 (3H, t, J = 7.2 Hz), 4.12 (2H, q, J = 6.9 Hz), 5.42 (2H, d, J = 47.5 Hz), 7.96 (1H, s). MS $^m/_z$: 225 (M+1).

(b) Etil 6-cloro-5-ciano-2-(fluorometil)nicotinato

Cloruro de oxalilo (5.49 mL, 64.9 mmol) y DMF (0.5 mL, 6.5 mmol) se agregaron a una solución de etil 5-ciano-2-(fluorometil)-6-oxo-1,6-dihidropiridin-3-carboxilato (3.0 g, 12.98 mmol) en DCM (120 mL) y la mezcla se calentó a reflujo durante 6 horas. El disolvente se evaporó y el residuo se disolvió en EtOAc/agua. Las fases se separaron y la fase orgánica se lavó con salmuera y $NaHCO_3$ (acuosa). La fase acuosa se

extrajo con EtOAc (dos veces) y la fase orgánica combinada se concentró para producir etil 6-cloro-5-ciano-2-(fluorometil)nicotinato como un sólido crema, el cual se utilizó sin purificación adicional. Rendimiento: 2.92 g (90%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33 (t, J = 7.1 Hz, 3H), 4.34 (q, J = 7.1 Hz, 2H), 5.88 (s, 1H), 5.77 (s, 1H), 8.89 (s, 1H). MS $^m/_z$: 243 (M+1).

(c) Etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(fluorometil)nicotinato

TEA (326 mg, 3.23mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(fluorometil)nicotinato (200mg, 0.81 mmol) y N-(bencilsulfonil) piperidin-4-carboxamida (251 mg, 0.89 mmol) en CH_3CN (1.5 mL) y 95% EtOH (2.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$ (dos veces). La fase acuosa combinada se extrajo con DCM y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 40% CH_3CN a 100% CH3CN/(0.1% HCOOH(acuoso)) produjo etil 6-(4-{[(bencilsulfonil)amino] carbonil}piperidin-1-il)-5-ciano-2-(fluorometil) nicotinato como un sólido crema. Rendimiento: 257 mg (65%).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.71 - 1.56 (2H, m), 1.89 - 1.79 (2H, m), 2.65-2.54 (1H, m), 3.24 - 3.12 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.64 - 4.53 (2H, m), 4.68 (2H, s), 5.63 (1H, s), 5.75 (1H, s), 7.33 - 7.23 (2H, m), 7.44 - 7.34 (3H, m), 8.40 (1H, s), 11.60 (1H, S). MS $^m/_z$: 489 (M+1).

Ejemplo 154

Etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(fluorometil)nicotinato

TEA (326 mg, 3.23mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(fluorometil)nicotinato (200mg, 0.81 mmol) y N-(bencilsulfonil)azetidin-3-carboxamida (225 mg, 0.89 mmol) en CH_3CN (1.5 mL) y 95% EtOH (2.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$. La fase acuosa combinada se extrajo con DCM y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 40% CH_3CN a 100% CH_3CN/(0.1% HCOOH(acuoso)) produjo etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(fluorometil)nicotinato como un sólido crema. Rendimiento: 221 mg (59%).

^{1}H NMR (400MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.62 - 3.51 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.39 - 4.29 (2H, m), 4.51 - 4.39 (2H, m), 4.74 (2H, s), 5.61 (1H, s), 5.73 (1H, s), 7.42 - 7.29 (5H, m), 8.38 (1H, s), 11.81 (1H, s). MS $^m/_z$: 461 (M+1).

Ejemplo 155

Etil 5-ciano-2-(difluorometil)-6-{4-[({[(4-metilciclohexil)metil]sulfonil}amino)carbonil]piperidin-1-il}nicotinato

(a) Ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il] piperidin-4-carboxílico

TEA (423 mg, 4.18 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(difluorometil)nicotinato (290 mg, 1.05 mmol) y ácido piperidin-4-carboxílico (148 mg, 1.15 mmol) en agua/EtOH (4.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 10 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$. La fase acuosa combinada se extrajo con DCM (dos veces) y la fase orgánica combinada se filtró a través de un separador de fase y se concentró para producir ácido 1-[3-ciano-6-(difluorometil)-5-

(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico como un sólido blanco, el cual se utilizó sin purificación adicional. Rendimiento: 356 mg (94%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, *J* = 7.2 Hz), 1.84-1.97 (2H, m), 2.08-2.17 (2H, m), 2.69-2.79 (1H, m), 3.37-3.47 (2H, m), 4.37 (2H, q, *J* =7.2 Hz), 4.61-4.70 (2H, m), 7.39 (1H, t, C<u>H</u>F_2), 8.43 (1H, s). MS ^{m}/z: 354 (M + 1).

(b) Etil 5-ciano-2-(difluorometil)-6-{4-[({[(4-metilciclohexil)metil] sulfonil}amino)carbonil]piperidin-1-il}nicotinato

DIPEA (64 mg, 0.5 mmol) se agregó a una solución de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico (35.3 mg, 0.1mmol) y TBTU (38.5 mg, 0.12mmol) en DCM (5mL) y la mezcla se agitó durante 30 minutos a temperatura de la sala antes de agregar 1-(4-metilciclohexil)metanosulfonamida (23 mg, 0.12mmol) disuelta en DCM (1 mL). La reacción se dejó agitar de un día para otro. LC-MS mostró que quedó material de partida, de modo que se agregaron más TBTU (19 mg, 0.06mmol) y DIPEA (26 mg, 0.2mmol) a la mezcla y la agitación se continuó durante otras 2 horas. La mezcla de reacción se lavó con 1% $KHSO_4$, la fase acuosa se extrajo con DCM (1ml) y las fases orgánicas combinadas se pasaron a través de un separador de fase y se evaporaron en una centrífuga de vacío. El producto crudo obtenido se purificó mediante HPLC (Kromasil C_8, empleando una gradiente de 20% a 100% CH_3CN/0.2% HOAc(acuoso)) para producir etil 5-ciano-2-(difluorometil)-6-{4-[({[(4-metilciclohexil)metil]sulfonil}amino)carbonil]piperidin-1-il}nicotinato como un sólido blanco. Rendimiento: 22mg (40%).

^{1}H NMR (400MHz, $CDCL_3$-d_6) δ 8.61 (1H, s), 8.42 (1H, s), 7.36 (1H, t, *J* = 54.3 Hz), 4.75 (2H, m), 4.35 (2H, q, *J* = 7.3 Hz), 3.46 (1H, m), 3.38 - 3.22 (3H, m), 2.59 (1H, m), 2.30 - 2.18 (1H, m), 2.10 - 1.97 (2H, m), 1.96 - 1.79 ($3H_5$ m), 1.75-1.47 (6H, m), 1.37 (3H, t, *J* = 7.2 Hz), 1.22 - 1.04 (2H, m), 0.92 - 0.83 (3H, m). MS ^{m}/z: 527 (M+1).

Ejemplo 156

Etil 5-ciano-2-(difluorometil)-6-[3-({[(2-fluorobencil)sulfonil] amino} carbonil)azetidin-1-il]nicotinato

(a) Ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il] azetidin-3-carboxílico

TEA (423 mg, 4.18 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(difluorometil)nicotinato (290 mg, 1.05 mmol) y ácido azetidin-3-carboxílico (116 mg, 1.15 mmol) en 95% EtOH (4.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 10 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$. La fase acuosa combinada se extrajo con DCM (dos veces) y la fase orgánica combinada se filtró a través de un separador de fase y se concentró para producir ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico como un sólido blanco, el cual se utilizó sin purificación adicional. Rendimiento: 359 mg (101%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J = 7.1 Hz), 3.62-3.72 (1H, m), 4.36 (2H, q, J =7.1 Hz), 4.63-4.75 (4H, m), 7.34 (1H, t, J = 54.2 Hz, C<u>H</u>F_2), 8.36 (1H, s). MS ^{m}/z: 326 (M + 1).

(b) Etil 5-ciano-2-(difluorometil)-6-[3-({[(2-fluorobencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato

DIPEA (64 mg, 0.5 mmol) se agregó a una solución de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico (32.5 mg, 0.1 mmol) y TBTU (38.5 mg, 0.12mmol) en DCM (5mL) y la mezcla se agitó durante 30 minutos a temperatura de la sala antes de agregar 1-(2-fluorofenil)metanosulfonamida (23 mg, 0.12mmol) disuelta en DCM (1 mL). La reacción se dejó agitar de un día para otro. LC-MS mostró que quedó material de partida, de modo que se agregaron más TBTU (19 mg, 0.06mmol) y DIPEA (26 mg, 0.2mmol) a la mezcla y la agitación se continuó durante otras 2 horas. La mezcla de reacción se lavó con 1% $KHSO_4$, la fase acuosa se extrajo con DCM (1ml) y las fases orgánicas

combinadas se pasaron a través de un separador de fase y se evaporó una centrífuga de gradiente. El producto crudo obtenido se purificó mediante HPLC (Kromasil C_8, empleando una gradiente de 20% a 100% CH_3CN/0.2% HOAc(acuoso)) para producir etil 5-ciano-2-(difluorometil)-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato como un sólido blanco. Rendimiento: 42mg (83%).

^{1}H NMR (400 MHz, $CDCL_3$-d_6) δ 1.38 (3H, t, J = 7.1 Hz), 3.50 - 3.40 (1H, m), 4.35 (2H, q, J = 7.2 Hz), 4.67 - 4.51 (4H, m), 4.72 (2H, s), 7.22 - 7.08 (2H, m), 7.46 - 7.34 (2H, m), 7.44 (1H, t, CHF_2), 8.35 (1H, s). MS ^{m}/z:497 (M + 1).

Ejemplo 157

Etil 5-ciano-2-(difluorometil)-6-[4-({[(2-fluorobencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(2-fluorofenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato. Rendimiento: 41 mg (78%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 6.8 Hz), 1.60 - 1.68 (2H, m), 1.85-1.90 (2H, m), 2.57 - 2.64 (1H, m), 3.17 - 3.24 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 4.53 - 4.58 (2H, m), 4.72 (2H, s), 7.20 - 7.26 (2H, m), 7.35-7.45 (2H, m), 7.37 (1H, t, J = 54.1 Hz), 8.47 (1H, s). MS m/z: 525 (M+1).

Ejemplo 158

Etil 5-ciano-2-(difluorometil)-6-[4-({[(3-fluorobencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(3-fluorofenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-

6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato.
Rendimiento: 21 mg (40%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.45 (1H, s), 7.35 (1H, t, J = 53.5 Hz), 7.38 - 7.43 (1H, m), 7.16 - 7.22 (1H, m), 7.05-7.11 (2H, m), 4.69 (2H, s), 4.48 - 4.55 (2H, m), 4.24 (2H, q, J = 7.1 Hz), 3.14 - 3.21 (2H, m), 2.53 - 2.58 (1H, m), 1.78 - 1.84 (2H, m), 1.56 - 1.65 (2H, m), 1.27 (3H, t, J = 7.1 Hz). MS $^m/_z$: 525 (M+1).

Ejemplo 159

Etil 5-ciano-2-(difluorometil)-6-[4-({[(4-fluorobencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(4-fluorofenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato.
Rendimiento: 19 mg (36%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.2 Hz), 1.58 - 1.67 (2H, m), 1.81 - 1.87 (2H, m), 3.15-3.22 (2H, m), 4.26 (2H, q, J = 7.1 Hz), 4.51 - 4.58 (2H, m), 4.66 (2H, s), 7.19 - 7.23 (2H, m), 7.28 - 7.32 (2H, m), 7.37 (1H, t, J = 54.1 Hz), 8.47 (1H, s).
¡Nota: Una H se oculta en la señal DMSO!
MS $^m/_z$: 525 (M+1).

Ejemplo 160

Etil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(2-clorofenil)metanosulfonamida para producir etil 6-[4-({[(2-clorobencil)

sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil) nicotinato. Rendimiento: 36 mg (67%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.2 Hz), 1.60 - 1.69 (2H, m), 1.86 - 1.92 (2H, m), 3.18 - 3.24 (2H, m), 4.25 (2H, q, J = 7.0 Hz), 4.51 - 4.59 (2H, m), 4.81 (2H, s), 7.26 - 7.53 (5H, m), 8.47 (1H, s).

¡Nota: Una H se oculta en la señal DMSO!

MS $^m/_z$: 541 (M+1).

Ejemplo 161

Etil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(3-clorofenil)metanosulfonamida para producir etil 6-[4-({[(3-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato. Rendimiento: 42 mg (78%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27 (3H, t, J = 6.8 Hz), 1.57 - 1.65 (2H, m), 1.78 - 1.84 (2H, m), 2.53 - 2.59 (1H, m), 3.14 - 3.21 (2H, m); 4.24 (2H, q, J = 6.9 Hz), 4.49 - 4.56 (2H, m), 4.68 (2H, s), 7.18 - 7.46 (5H, m), 8.46 (1H, s). MS $^m/_z$: 541 (M+1).

Ejemplo 162

Etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(4-clorofenil)metanosulfonamida para producir etil 6-[4-({[(4-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(difluorometil)nicotinato. Rendimiento: 33 mg (61%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.2 Hz), 1.58 - 1.72 (2H, m), 1.82 - 1.92 (2H, m), 2.56 - 2.68 (1H, m), 3.16 - 3.26 (2H, m), 4.28 (2H, q, J = 7.2 Hz), 4.52 - 4.61 (2H, m), 4.70 (2H, s), 7.28 - 7.35 (2H, m), 7.39 (1H, t, J = 54.1 Hz), 7.44 - 7.51 (2H, m), 8.50 (1H, s), 11.64 (1H, s). MS $^m/_z$: 541 (M+1).

Ejemplo 163

Etil 5-ciano-2-(difluorometil)-6-[4-({[(3-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(3-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato.
Rendimiento: 17 mg (32%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31 (3H, t, J = 7.3 Hz), 1.59 - 1.73 (2H, m), 1.79 - 1.89 (2H, m), 2.29 (3H, s), 2.54 - 2.64 (1H, m), 3.16 - 3.26 (2H, m), 4.28 (2H, q, J = 7.4 Hz), 4.53 - 4.61 (2H, m), 4.63 (2H, s), 7.04 - 7.10 (2H, m), 7.16 - 7.22 (1H, m), 7.24 - 7.31.(1H, m), 7.39 (1H, t, J = 53.9 Hz), 8.49 (1H, s), 11.59 (1H, s). MS $^m/_z$: 521 (M+1).

Ejemplo 164

Etil 5-ciano-2-(difluorometil)-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(4-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato.
Rendimiento: 19 mg (36%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 1.27 (3H, t, J = 7.2 Hz), 1.57 - 1.65 (2H, m), 1.79 - 1.85 (2H, m), 2.26 (3H, s), 3.14 - 3.21 (2H, m), 4.24 (2H, q, J =

7.3 Hz), 4.50 - 4.56 (2H, m), 4.58 (2H, s), 7.10 - 7.18 (4H, m), 7.36 (1H, t, *J* = 53.4 Hz), 8.46 (1H, s).

¡Nota: Una H se oculta en la señal DMSO!

MS $^{m}/_{z}$: 521 (M+1).

Ejemplo 165

Etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 1-(2,4-diclorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(difluorometil)nicotinato. Rendimiento: 27 mg (47%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, *J* = 7.0 Hz), 1.59 - 1.68 (2H, m), 1.87 - 1.93 (2H, m), 2.54 - 2.60 (1H, m), 3.18 - 3.24 (2H, m), 4.26 (2H, q, *J* = 6.8 Hz), 4.52 - 4.58 (2H, m), 4.81 (2H, s), 7.26 - 7.52 (3H, m), 7.69 (1H, s), 8.47 (1H, s). MS$^{m}/_{z}$: 575 (M+1).

Ejemplo 166

Etil 5-ciano-2-(difluorometil)-6-[3-({[(3-fluorobencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(3-fluorofenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato. Rendimiento: 47 mg (95%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, *J* = 7.3 Hz), 3.51 - 3.59 (1H, m), 4.25 (2H, q, *J* = 7.4 Hz), 4.26 - 4.51 (4H, m), 4.75 (2H, s), 7.12 - 7.22 (3H, m), 7.35-7.42 (1H, m), 7.37 (1H, t, *J* = 53.2 Hz), 8.44 (1H, s). MS $^{m}/_{z}$: 497 (M+1).

Ejemplo 167

Etil 5-ciano-2-(difluorometil)-6-[3-({[(4-fluorobencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(4-fluorofenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato.
Rendimiento: 41 mg (83%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.1 Hz), 3.49 - 3.57 (1H, m), 4.23 (2H, q, J = 7.1 Hz), 4.26 - 4.50 (4H, m), 4.69 (2H, s), 7.12 - 7.19 (2H, m), 7.32 - 7.37 (2H, m), 7.36 (1H, t, J = 54.2 Hz), 8.43 (1H, s). MS $^m/_z$: 497 (M+1).

Ejemplo 168

Etil 6-[3-({[(2-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(2-clorofenil)metanosulfonamida para producir etil 6-[3-({[(2-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil) nicotinato.
Rendimiento: 42 mg (82%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.58 - 3.68 (1H, m), 4.27 (2H, q, J = 7.5 Hz), 4.36 - 4.57 (4H, m), 4.90 (2H, s), 7.35-7.46 (2H, m), 7.40 (1H, t, J = 54.2 Hz), 7.47 - 7.56 (2H, m), 8.47 (1H, s), 12.03 (1H, s). MS $^m/_z$: 513 (M+1).

Ejemplo 169

Etil 6-[3-({[(3-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(3-clorofenil)metanosulfonamida para producir etil 6-[3-({[(3-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato.
Rendimiento: 46 mg (90%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.1 Hz), 3.51 - 3.59 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.25-4.54 (4H, m), 4.76 (2H, s), 7.26 - 7.30 (1H, m), 7.35-7.47 (4H, m), 8.44 (1H, s). MS $^m/_z$: 513 (M+1).

Ejemplo 170

Etil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A´ de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(4-clorofenil)metanosulfonamida para producir etil 6-[3-({[(4-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(difluorometil)nicotinato.
Rendimiento: 45 mg (88%).
^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.0 Hz), 3.50 - 3.57 (1H, m), 4.23 (2H, q, J = 7.0 Hz), 4.27 - 4.50 (4H, m), 4.70 (2H, s), 7.30 - 7.34 (2H, m), 7.36 (1H, t, J = 53.8 Hz), 7.38 - 7.43 (2H, m), 8.43 (1H, s). MS $^m/_z$: 513 (M+1).

Ejemplo 171

Etil 5-ciano-2-(difluorometil)-6-[3-({[(3-metilbencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(3-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato.
Rendimiento: 36 mg (73%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.6 Hz), 2.22 (3H, s), 3.48 - 3.56 (1H, m), 4.23 (2H, q, J = 7.0 Hz), 4.24 - 4.49 (4H, m), 4.64 (2H, s), 7.06 - 7.10 (2H, m), 7.12 - 7.16 (1H, m), 7.19 - 7.23 (1H, m), 7.36 (1H, t, J = 54.9 Hz), 8.43 (1H, s). MS $^m/_z$: 493 (M+1).

Ejemplo 172

Etil 5-ciano-2-(difluorometil)-6-[3-({[(4-metilbencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(4-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato. Rendimiento: 31 mg (63%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 6.9 Hz), 2.24 (3H, s), 3.47 - 3.55 (1H, m), 4.23 (2H, q, J = 6.9 Hz), 4.26 - 4.49 (4H, m), 4.63 (2H, s), 7.11 - 7.19 (4H, m), 7.36 (1H, t, J = 53.8 Hz), 8.43 (1H, s). MS $^m/_z$: 493 (M+1).

Ejemplo 173

Etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(2,4-diclorofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil)nicotinato. Rendimiento: 7 mg (12%).

^{1}H NMR (600 MHz, DMSO-d_6) δ 1.26 (3H, t, J = 7.3 Hz), 3.44 - 3.55 (1H, m), 4.23 (2H, q, J = 7.3 Hz), 4.29 - 4.52 (4H, m), 4.67 - 4.83 (2H, m), 7.35 (1H, t, J = 54.3 Hz), 7.38 - 7.50 (2H, m), 7.57 - 7.64 (1H, m), 8.42 (1H, s). MS $^m/_z$: 547 (M+1).

Ejemplo 174

Etil 5-ciano-2-(difluorometil)-6-{3-[({[(4-metilciclohexil)metil]sulfonil} amino)carbonil]azetidin-1-il}nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(4-metilciclohexil)metanosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-{3-[({[(4-etilciclohexil)metil]sulfonil}amino)carbonil] azetidin-1-il}nicotinato. Rendimiento: 27 mg (55%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 - 0.95 (3H, m), 1.01 - 1.20 (2H, m), 1.30 (3H, t, *J* = 7.0 Hz), 1.40 - 1.58 (5H, m), 1.60 - 1.88 (2H, m), 2.04 - 2.15 (1H, m), 3.40 - 3.45 (2H, m), 3.59 - 3.69 (1H, m), 4.26 (2H, q, *J* = 7.4 Hz), 4.33 - 4.58 (4H, m), 7.38 (1H, t, *J* = 54.3 Hz), 8.46 (1H, s), 11.93 (1H, s). MS $^m/_z$: 499 (M+1).

Ejemplo 175

Etil 5-ciano-6-[3-({[(3-cianofenil)sulfonil]amino}carbonil) azetidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 3-cianobencenosulfonamida para producir etil 5-ciano-6-[3-({[(3-cianofenil) sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil)nicotinato.
Rendimiento: 47 mg (64%). MS ^{m}/z: 490 (M +1).

Ejemplo 176

Etil 5-ciano-6-[3-({[(4-cianofenil)sulfonil]amino}carbonil) azetidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 4-

cianobencenosulfonamida para producir etil 5-ciano-6-[3-({[(4-cianofenil) sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil)nicotinato. Rendimiento: 42 mg (57%). MS $^{m}/_{z}$: 490 (M +1).

Ejemplo 177

Etil 5-ciano-2-(difluorometil)-6-{3-[({[4-(trifluorometoxi)fenil]sulfonil} amino)carbonil]azetidin-1-il}nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 4-(trifluorometoxi)bencenosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-{3-[({[4-(trifluorometoxi)fenil]sulfonil}amino) carbonil]azetidin-1-il}nicotinato. Rendimiento: 37 mg (45%). MS $^{m}/_{z}$: 549 (M +1).

Ejemplo 178

Etil 5-ciano-2-(difluorometil)-6-{3-[({[2-(trifluorometoxi)fenil] sulfonil} amino)carbonil]azetidin-1-il}nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 2-(trifluorometoxi)bencenosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-{3-[({[2-(trifluorometoxi)fenil]sulfonil}amino) carbonil]azetidin-1-il}nicotinato. Rendimiento: 44 mg (53%). MS $^{m}/_{z}$: 549 (M +1).

Ejemplo 179

Etil 5-ciano-6-[3-({[(2-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y 1-(2-

cianofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(2-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(difluorometil) nicotinato. Rendimiento: 52 mg (69%). MS ^{m}/z: 504 (M +1).

Ejemplo 180

Etil 5-ciano-2-(difluorometil)-6-(3-{[(2-naftilsulfonil)amino] carbonil} azetidin-1-il)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y naftalen-2-sulfonamida para producir etil 5-ciano-2-(difluorometil)-6-(3-{[(2-naftilsulfonil)amino]carbonil}azetidin-1-il)nicotinato. Rendimiento: 48 mg (62%). MS $^{m}/_{z}$: 515 (M +1).

Ejemplo 181

Etil 6-(3-{[(butilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]azetidin-3-carboxílico y butan-1-sulfonamida para producir etil 6-(3-{[(butilsulfonil)amino]carbonil} azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato. Rendimiento: 44 mg (65%). MS ^{m}/z: 445 (M +1).

Ejemplo 182

Etil 5-ciano-6-[4-({[(3-cianofenil)sulfonil]amino}carbonil) piperidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico 3-cianobencenosulfonamida para producir etil 5-ciano-6-[4-({[(3-cianofenil)

sulfonil]amino}carbonil)piperidin-1-il]-2-(difluorometil)nicotinato. Rendimiento: 9 mg (12%). MS $^{m}/_{z}$: 518 (M +1).

Ejemplo 183

Etil 5-ciano-6-[4-({[(4-cianofenil)sulfonil]amino}carbonil)piperidin-1-il]-2-(difluorometil)nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 4-cianobencenosulfonamida para producir etil 5-ciano-6-[4-({[(4-cianofenil) sulfonil]amino}carbonil)piperidin-1-il]-2-(difluorometil)nicotinato. Rendimiento: 9 mg (12%). MS $^{m}/_{z}$: 518 (M +1).

Ejemplo 184

Etil 5-ciano-2-(difluorometil)-6-{4-[({[4-(trifluorometoxi)fenil]sulfonil} amino)carbonil]piperidin-1-il}nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 4-(trifluorometoxi)bencenosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-{4-[({[4-(trifluorometoxi)fenil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato. Rendimiento: 17 mg (19%). MS ^{m}/z: 577 (M + 1).

Ejemplo 185

Etil 5-ciano-2-(difluorometil)-6-{4-[({[2-(trifluorometoxi)fenil]sulfonil} amino)carbonil]piperidin-1-il}nicotinato

Preparado de acuerdo con el método A' de ácido 1-[3-ciano-6-(difluorometil)-5-(etoxicarbonil)piridin-2-il]piperidin-4-carboxílico y 2-(trifluorometoxi)bencenosulfonamida para producir etil 5-ciano-2-(difluorometil)-6-{4-[({[2-(trifluorometoxi)fenil]sulfonil}amino)

carbonil}piperidin-1-il)-5-ciano-2-(difluorometil)nicotinato. Rendimiento: 36 mg (51%). MS ^{m}/z: 473 (M +1).

Ejemplo 189

Etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}pirrolidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

(a) Ácido {1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il] pirrolidin-3-il}acético

TEA (606 mg, 5.99 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato (341mg, 1.2 mmol) y ácido pirrolidin-3-ilacético (209 mg, 1.62 mmol) en agua/EtOH (4.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$. La fase acuosa combinada se extrajo con DCM y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 5% CH_3CN a 100% CH_3CN/(0.2% HOAc(acuoso)) produjo ácido {1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]pirrolidin-3-il}acético como un sólido blanco. Rendimiento: 219 mg (49%).
^{1}H NMR (400MHz, $CDCL_3$) δ 1.35 (3H, t, *J* = 7.2 Hz), 1.85-1.68 (1H, m), 2.38 - 2.23 (1H, m), 2.64 - 2.47 (2H, m), 2.81 - 2.66 (1H, m), 3.57 - 3.40 (1H, m), 3.91 - 3.77 (1H, m), 4.08 - 3.97 (1H, m), 4.21 - 4.10 (1H, m), 4.33 (2H, q, *J* = 7.3 Hz), 8.31 (1H, s). MS ^{m}/z: 371 (M+1).

(b) Etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}pirrolidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método B' de ácido {1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]pirrolidin-3-il}acético y 1-fenilmetanosulfonamida para producir etil 6-(3-{2-[(bencilsulfonil)amino]-

2-oxoetil}pirrolidin-1-il)-5-ciano-2-(trifluorometil)nicotinato.

Rendimiento: 88 mg (84%).

^{1}H NMR (600 MHz, DMSO) d 1.26 (3H, t, J = 7.3 Hz), 1.59-1.68 (1H, m), 2.09-2.17 (1H, m), 2.40-2.44 (2H, m), 3.64-3.77 (1H, m), 3.81-3.91 (1H, m), 3.94-4.06 (1H, m), 4.24 (2H, q, J = 7.0 Hz), 4.68 (2H, s), 7.24-7.39 (5H, m), 8.45 (1H, s).

¡Nota: Un H oculto en el pico DMSO y un H oculto en el pico H_2O!

MS $^m/_z$: 525 (M+1).

Ejemplo 190

Etil 5-ciano-6-[3-(2-oxo-2-{[(2-feniletil)sulfonil]amino}etil)pirrolidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método B' de ácido {1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]pirrolidin-3-il}acético y 2-feniletanosulfonamida para producir etil 5-ciano-6-[3-(2-oxo-2-{[(2-feniletil)sulfonil]amino}etil)pirrolidin-1-il]-2-(trifluorometil)nicotinato.

Rendimiento: 73 mg (68%).

^{1}H NMR (600 MHz, DMSO) d 1.25 (3H, t, J = 7.0 Hz), 1.58 - 1.66 (1H, m), 2.05-2.13 (1H, m), 2.37 - 2.40 (2H, m), 2.92 - 2.98 (2H, m), 3.62 - 3.67 (2H, m), 3.67 - 3.75 (1H, m), 3.80 - 3.99 (2H, m), 4.23 (2H, q, J = 7.3 Hz), 7.15-7.31 (5H, m), 8.43 (1H, s).

¡Nota: Un H oculto en el pico DMSO y un H oculto en el pico H_2O!

MS $^m/_z$: 537 (M-1)

sulfonil]amino}-2-oxoetil)pirrolidin-1-il]-5-ciano-2-(trifluorometil) nicotinato. Rendimiento: 86 mg (78%).

^{1}H NMR (500 MHz, DMSO) d 1.29 (3H, t, J = 6.9 Hz), 1.60 - 1.69 (1H, m), 2.06 - 2.14 (1H, m), 2.44 - 2.48 (1H, m), 2.55-2.60 (1H, m), 3.33 - 3.39 (1H, m), 3.68 - 3.76 (1H, m), 3.84 - 3.96 (2H, m), 4.28 (2H, q, J = 7.2 Hz), 7.22 (1H, d, J = 4.2 Hz), 7.63 (1H, d, J = 4.2 Hz), 8.41 (1H, S). MS $^m/_z$: 549 (M-1).

Ejemplo 192

Etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato

(a) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il] azetidin-3-carboxílico

TEA (0.908 g, 8.97 mmol) se agregó a una suspensión de etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato (1.0 g, 3.59 mmol) y ácido azetidin-3-carboxílico (0.399 g, 3.95 mmol) en EtOH (10 mL) y la mezcla se calentó en un horno microondas de nodo simple durante 20 minutos. El disolvente se evaporó y el residuo se repartió en porciones entre iPrOAc (10 mL)/agua y Na_2CO_3. La fase acuosa se separó y se acidificó mediante la adición de HCl concentrado. La fase acuosa ácida se extrajo con iPrOAc (2 x 10 mL). Los extractos combinados se secaron (MgSO4) y se evaporaron para producir ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico como un sólido marrón, el cual se utilizó sin purificación adicional. Rendimiento: 1.04 g (84%).

^{1}H-NMR (500 MHz, DMSO-d_6) δ 1.27 (3H, t, J = 7.1 Hz), 3.55-3.62 (1H, m), 4.28 (2H, q, J = 7.1 Hz), 4.38-4.58 (4H, m), 8.46 (1H, s).

(b) Etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil) nicotinato.
MS $^m/z$: 515 (M +1).

Ejemplo 193

Etil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(3-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil) nicotinato.
MS $^m/_z$: 515 (M +1).

Ejemplo 194

Etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(2-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil) nicotinato.
MS $^m/_z$: 515 (M +1).

Ejemplo 195

Etil 5-ciano-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-metilfenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil) nicotinato.
MS $^{m}/_{z}$: 511 (M +1).

Ejemplo 196

Etil 5-ciano-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(3-metilfenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil) nicotinato.
MS $^{m}/_{z}$: 511 (M +1).

Ejemplo 197

Etil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-clorofenil)metanosulfonamida para producir etil 6-[3-({[(4-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil) nicotinato.
MS $^{m}/_{z}$: 531 (M +1).

Ejemplo 198

Etil 6-[3-({[(2-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(2-clorofenil)metanosulfonamida para producir etil 6-[3-({[(2-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil) nicotinato.
MS $^m/z$: 531 (M +1).

Ejemplo 199

Etil 6-[3-({[(3-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(3-clorofenil)metanosulfonamida para producir etil 6-[3-({[(3-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(trifluorometil) nicotinato.
MS $^m/_z$: 531 (M +1).

Ejemplo 200

Etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(2,4-diclorofenil)metanosulfonamida para producir etil etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(trifluorometil) nicotinato.
MS $^m/z$: 565 (M +1).

Ejemplo 201

Etil 6-(3-{[(5-cloro-2-tienil)sulfonil]carbamoil}azetidin-1-il)-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método D' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]azetidin-3-carboxílico y 5-clorotiofen-2-sulfonamida para producir etil 6-(3-{[(5-cloro-2-tienil) sulfonil]carbamoil}azetidin-1-il)-5-ciano-2-(trifluorometil)nicotinato. MS $^{m}/_{z}$: 523 (M +1).

Ejemplo 202

Etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato

(a) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-trifluorometil)piridin-2-il] piperidin-4-carboxílico

TEA (0.908 g, 8.97 mmol) se agregó a una suspensión de etil 6-cloro-5-ciano-2-(trifluorometil)nicotinato (1.0 g, 3.59 mmol) y ácido piperidin-4-carboxílico (0.510 g, 3.95 mmol) en EtOH (10 mL) y la mezcla se calentó en un horno microondas de nodo simple durante 15 minutos. El disolvente se evaporó y el residuo se repartió en porciones entre iPrOAc (10 mL)/agua y 20% Na_2CO_3 (1 mL). La fase acuosa se separó, se agregó1 mL EtOH y la fase acuosa se acidificó mediante la adición HCl de concentrado. La fase acuosa ácida se extrajo con iPrOAc (2 x 10 mL). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró para producir ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico como un sólido café, el cual se utilizó sin purificación adicional. Rendimiento: 1.06 g (79%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 1.28 (3H, t, J = 7.1 Hz), 1.61-1.71 (2H, m), 1.95-2.02 (2H, m), 2.60-2.68 (1H, m), 3.31-3.38 (2H, m), 4.28 (2H, q, J = 7.1 Hz), 4.41-4.48 (2H, m), 8.51 (1H, S).

(b) Etil 5-ciano-6-[4-({[(4-fluorobencilsulfonil]amino}carbonil) piperidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil) nicotinato. Rendimiento: 4.3 mg (4%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7 Hz), 1.78-1.94 (4H, m), 2.49-2.55 (1H, m), 3.23 (2H, t, J = 12.5 Hz), 4.35 (2H, q, J = 7 Hz), 4.60 (2H, s), 4.67 (2H, br d, J = 12.5 Hz), 7.06 (2H, t, J = 8.5 Hz), 7.31 (2H, dd, J = 5, 8.5 Hz), 8.34 (1H, s), 9.50 (1H, s).

MS $^m/_z$: 543 (M+1).

Ejemplo 203

Etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(3-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil) nicotinato. Rendimiento: 5.7 mg (5%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 1.81-1.97 (4H, m), 2.53-2.61 (1H, m), 3.28 (2H, t, J = 12.5 Hz), 4.39 (2H, q, J = 7.5 Hz), 4.67 (2H, s), 4.71 (2H, br d, J = 12.5 Hz), 7.12-7.15 (3H, m), 7.36-7.41 (1H, m), 8.38 (1H, s), 9.68 (1H, s). MS $^m/_z$: 543 (M+1).

Ejemplo 204

Etil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(2-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(2-

fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil) nicotinato. Rendimiento: 5.1 mg (5%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, t, *J* = 6.5 Hz), 1.80-1.99 (4H, m), 2.53-2.61 (1H, m), 3.27 (2H, t, *J* = 13 Hz), 4.34 (2H, q, *J* = 6.5 Hz), 4.67 (2H, br d, *J* = 13 Hz), 4.69 (2H, s), 7.11 (1H, t, *J* = 9 Hz), 7.17 (1H, t, *J* = 7.5 Hz), 7.34-7.39 (2H, m), 8.33 (1H, s), 9.63 (1H, s). MS $^m/_z$: 543 (M+1).

Ejemplo 205

Etil 5-ciano-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-metilfenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil) nicotinato. Rendimiento: 3.4 mg (3%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (3H, t, *J* = 7.5 Hz), 1.75-1.93 (4H, m), 2.34 (3H, s), 2.44-2.52 (1H, m), 3.23 (2H, t, *J* = 12.5 Hz), 4.35 (2H, q, *J* = 7.5 Hz), 4.58 (2H, s), 4.66 (2H, br d, *J* = 12.5 Hz), 7.15-7.21 (4H, m), 8.33 (1H, s), 8.88 (1H, s). MS $^m/_z$: 539 (M+1).

Ejemplo 206

Etil 5-ciano-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(3-metilfenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil) nicotinato. Rendimiento: 2.8 mg (3%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* = 7.5 Hz), 1.71-1.88 (4H, m), 2.28 (3H, s), 2.39- 2.47 (1H, m), 3.18 (2H, t, *J* = 13 Hz), 4.30 (2H, q, *J* =

7.5 Hz), 4.54 (2H, s), 4.61 (2H, br d, J = 13 Hz), 7.05-7.23 (4H, m), 8.29 (1H, s), 8.72 (1H, s). MS $^{m}/_{z}$: 539 (M+1).

Ejemplo 207

Etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-clorofenil)metanosulfonamida para producir etil 6-[4-({[(4-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil) nicotinato. Rendimiento: 6.6 mg (6%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 7.5 Hz), 1.63-1.70 (2H, m), 1.74-1.79 (2H, m), 2.39-2.41 (1H, m), 3.09 (2H, t, J = 12.5 Hz),4.18 (2H, q, J = 7.5 Hz), 4.42 (2H, s), 4.52 (2H, br d, J = 12.5 Hz), 7.12 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.5 Hz), 8.18 (1H, s), 11.32 (1H, s). MS $^{m}/_{z}$: 559 (M+1)

Ejemplo 208

Etil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(2-clorofenil)metanosulfonamida para producir etil 6-[4-({[(2-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato. Rendimiento: 7.8 mg (7%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 7 Hz), 1.81-1.90 (2H, m), 1.96-2.00 (2H, m), 2.56-2.64 (1H, m), 3.26 (2H, 1, J = 12 Hz),4.34 (2H, q, J = 7 Hz), 4.68 (2H, br d, J = 12 Hz), 4.84 (2H, s), 7.27-7.34 (2H, m), 7.42 (2H, t, J = 7 Hz), 8.34 (1H, s), 10.03 (1H, s). MS $^{m}/_{z}$: 559 (M+1).

Ejemplo 209

Etil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(3-clorofenil)metanosulfonamida para producir etil 6-[4-({[(3-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil) nicotinato. Rendimiento: 7.3 mg (6%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (3H, t, J = 7.5 Hz), 1.81-1.90 (2H, m), 1.91-1.97 (2H, m), 2.54-2.62 (1H, m), 3.28 (2H, t, J = 12.5 Hz), 4.39 (2H, q, J = 7.5 Hz), 4.64 (2H, s), 4.72 (2H, br d, J = 12.5 Hz), 7.25 (1H, d, J = 7.5 Hz), 7.34-7.42 (3H, m), 8.38 (1H, s), 10.02 (1H, s). MS $^m/_z$: 559 (M+1).

Ejemplo 210

Etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(2,4- diclorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(trifluorometil)nicotinato. Rendimiento: 5.5 mg (5%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 7.5 Hz), 1.83-1.90 (2H, m), 1.97-2.01 (2H, m), 2.56-2.64 (1H, m), 3.29 (2H, t, J = 12.5 Hz), 4.34 (2H, q, J = 7.5 Hz), 4.68 (2H, br d, J = 12.5 Hz), 4.80 (2H, s), 7.28 (1H, dd, J = 2, 8.5 Hz), 7.37 (1H, d, J = 8.5 Hz), 7.45 (1H, d, J = 2 Hz), 8.33 (1H, s), 10.04 (1H, s). MS $^m/_z$: 593 (M+1).

Ejemplo 211

Etil 6-[4-({[(5-cloro-2-tienil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil)nicotinato

Preparado de acuerdo con el método C' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(trifluorometil)piridin-2-il]piperidin-4-carboxílico y 5-clorotiofen-2-sulfonamida para producir etil 6-[4-({[(5-cloro-2-tienil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(trifluorometil) nicotinato. Rendimiento: 19.1 mg (17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7 Hz), 1.72-1.84 (2H, m), 1.91-1.97 (2H, m), 2.55-2.65 (1H, m), 3.27 (2H, t, J = 12.5 Hz), 4.33 (2H, q, J = 7.5 Hz), 4.61 (2H, br d, J = 12.5 Hz), 6.91 (1H, d, J = 4 Hz), 7.62 (1H, d, J = 4 Hz), 8.30 (1H, s), 10.99 (1H, s). MS $^m/_z$: 551 (M+1).

Ejemplo 212

Etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(fluorometil)nicotinato

(a) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il] azetidin-3-carboxílico

TEA (653 mg, 6.46 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(fluorometil)nicotinato (400mg, 1.61 mmol) y ácido azetidin-3-carboxílico (179 mg, 1.78 mmol) en agua/EtOH (4.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$. La fase acuosa se extrajo con DCM y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 5% CH_3CN a 100% CH_3CN/(0.2% HOAc(acuoso)) produjo ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico como un sólido blanco. Rendimiento: 302 mg (60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, t, J = 7.3 Hz), 3.59-3.69 (1H, m), 4.31 (2H, q, J = 7.3 Hz), 4.60-4.70 (4H, m), 5.69 (2H, d, J = 47.3 Hz), 8.30 (1H, br s).

(b) Etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(2-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 21 mg (44%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.55-3.66 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.34 - 4.44 (2H, m), 4.43 - 4.56 (2H, m), 4.80 (2H, s), 5.68 (2H, d, J = 47.1 Hz), 7.18 - 7.32 (2H, m), 7.37 - 7.52 (2H, m), 8.39 (1H, s), 11.80 - 12.19 (1H, m). MS ^{m}/z: 479 (M+1).

Ejemplo 213

Etil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(3-fluorofenil) metanosulfonamida para producir etil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 25 mg (53%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 3.54 - 3.64 (1H, m), 4.24 (2H, q, J= 7.1 Hz), 4.28 - 4.36 (2H, m), 4.39 - 4.53 (2H, m), 4.79 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.13 - 7.27 (3H, m), 7.37 - 7.47 (1H, m), 8.38 (1H, s), 11.55-12.36 (1H, m). MS ^{m}/z: 479 (M+1).

Ejemplo 214

Etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-fluorofenil) metanosulfonamida para producir etil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 27 mg (56%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.55-3.77 (1H, m), 4.24 (2H, q, J = 7.1 Hz), 4.29 - 4.37 (2H, m), 4.41 - 4.51 (2H, m), 4.73 (2H, s), 5.66 (2H, d, J = 47.1 Hz), 7.15-7.23 (2H, m), 7.34 - 7.42 (2H, m), 8.37 (1H, s). MS $^m/_z$: 479 (M+1).

Ejemplo 215

Etil 6-[3-({[(2-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(2-clorofenil)metanosulfonamida para producir etil 6-[3-({[(2-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato. Rendimiento: 13 mg (27%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.59 - 3.69 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.36 - 4.56 (4H, m), 4.90 (2H, s), 5.67 (2H, d, J = 47.3 Hz), 7.34 - 7.56 (4H, m), 8.38 (1H, s), 11.73 - 12.28 (1H, m). MS $^m/_z$: 495 (M+1).

Ejemplo 216

Etil 6-[3-({[(3-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(3-clorofenil)metanosulfonamida para producir etil 6-[3-({[(3-clorobencil)

sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato.
Rendimiento: 28 mg (58%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 3.51 - 3.65 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.27 - 4.37 (2H, m), 4.40 - 4.53 (2H, m), 4.79 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.27 - 7.50 (4H, m), 8.36 - 8.40 (1H, m), 11.71 - 12.13 (1H, m). MS $^m/_z$: 495 (M+1).

Ejemplo 217

Etil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-clorofenil)metanosulfonamida para producir etil 6-[3-({[(4-clorobencil) sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-(fluorometil)nicotinato.
Rendimiento: 33 mg (68%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.45-3.58 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.29 - 4.38 (2H, m), 4.38 - 4.50 (2H, m), 4.60 (2H, s), 5.66 (2H, d, J = 47.1 Hz), 7.29 - 7.41 (4H, m), 8.36 (1H, s). MS $^m/_z$: 495 (M+1).

Ejemplo 218

Etil 5-ciano-2-(fluorometil)-6-[3-({[(3-metilbencil)sulfonil]amino} carbonil) azetidin-1-il]nicotinato

Preparado de acuerdo con el método E´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(3-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(fluorometil)-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato.
Rendimiento: 41 mg (86%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 2.27 (3H, s), 3.51 - 3.60 (1H, M), 4.25 (2H, q, J = 7.2 Hz), 4.29 - 4.37 (2H, m), 4.39 -

4.51 (2H, m), 4.69 (2H, s), 5.67 (2H, d, J = 50.0 Hz), 7.07 - 7.32 (4H, m), 8.38 (1H, s), 11.59 - 12.03 (1H, m). MS ^{m}/z: 475 (M+1).

Ejemplo 219

Etil 5-ciano-2-(fluorometil)-6-[3-({[(4-metilbencil)sulfonil]amino} carbonil)azetidin-1-il]nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(fluorometil)-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato.
Rendimiento: 12 mg (25%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 2.28 (3H, s), 3.53 - 3.60 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.29 - 4.36 (2H, m), 4.39 - 4.50 (2H, m), 4.67 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.15-7.23 (4H, m), 8.37 - 8.40 (1H, m), 11.48 - 12.04 (1H, m). MS ^{m}/z: 475 (M+1).

Ejemplo 220

Etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(2,4-diclorofenil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 27 mg (51%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 3.56 - 3.65 (1H, m), 4.24 (2H, q, J = 7.2 Hz), 4.35-4.58 (4H, m), 4.86 (2H, s), 5.67 (2H, d, J = 47.1 Hz), 7.41 - 7.70 (3H, m), 8.36 - 8.39 (1H, m). MS $^{m}/_{z}$: 529 (M+1).

Ejemplo 221

Etil 5-ciano-2-(fluorometil)-6-{3-[({[(4-metilciclohexil)metil]sulfonil} amino)carbonil]azetidin-1-il}nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico y 1-(4-metilciclohexil)metanosulfonamida para producir etil 5-ciano-6-[3-({[(2,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 28 mg (57%).

^{1}H NMR (400MHz, DMSO-d_6) δ 0.75-0.92 (4H, m), 0.95-1.17 (3H, m), 1.25 (3H, t, J = 7.1 Hz), 1.35-1.54 (4H, m), 1.55-1.64 (1H, m), 1.74 - 1.84 (1H, m), 2.00 - 2.10 (1H, m), 3.22 - 3.28 (1H, m), 3.51 - 3.63 (1H, m), 4.20 (2H, q, J = 7.1 Hz), 4.29 - 4.39 (2H, m), 4.40 - 4.51 (2H, m), 5.61 (2H, d, J = 47.3 Hz), 8.32 (1H, s). MS $^m/_z$: 481 (M+1).

Ejemplo 222

Etil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil)nicotinato

(a) Ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il] piperidin-4-carboxílico

TEA (653 mg, 6.46 mmol) se agregó a una solución de etil 6-cloro-5-ciano-2-(fluorometil)nicotinato (400mg, 1.61 mmol) y ácido piperidin-4-carboxílico (229 mg, 1.78 mmol) en agua/EtOH (4.5 mL). La mezcla se calentó en un horno microondas de nodo simple a 120 °C durante 20 minutos. El disolvente se evaporó y el residuo se tomó en DCM y se lavó con 1% $KHSO_4$. La fase acuosa se extrajo con DCM y la fase orgánica combinada se filtró a través de un separador de fase y se concentró. Purificación mediante HPLC (Kromasil C8, Eluyente: Una gradiente de 5% CH_3CN a 100% CH_3CN/(0.2% HOAc(acuoso)) produjo ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]azetidin-3-carboxílico como un sólido blanco. Rendimiento: 76 mg (14%).

^{1}H NMR (400 MHz, $CDCL_3$) δ 1.36 (3H, t, *J* = 7.2 Hz), 1.82-1.94 (2H, m), 2.05-2.14 (2H, m), 2.66-2.76 (1H, m), 3.32-3.42 (2H, m), 4.31 (2H, t, *J* = 7.2 Hz), 4.61-4.69 (2H, m), 5.70 (2H, d, *J* = 47.3Hz), 8.36 (1H, br s).

(b) Etil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(2-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 13 mg (25%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, *J* = 7.1 Hz), 1.56 - 1.75 (2H, m), 1.82 - 1.93 (2H, m), 2.56 - 2.64 (1H, m), 3.14 - 3.26 (2H, m), 4.25 (2H, q, *J* = 7.1 Hz), 4.55-4.64 (2H, m), 4.68 (2H, s), 5.68 (2H, d, *J* = 47.1 Hz), 7.18 - 7.30 (2H, m), 7.32 - 7.48 (2H, m), 8.39 (1H, s). MS ^{m}/z: 507 (M+1).

Ejemplo 223

Etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(3-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 16 mg (31%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, *J* = 7.1 Hz), 1.56 - 1.71 (2H, m), 1.79 - 1.89 (2H, m), 2.55-2.61 (1H, m), 3.15-3.26 (2H, m), 4.25 (2H, q, *J* = 7.1 Hz), 4.53 - 4.64 (2H, m), 4.70 (2H, s), 5.69 (2H, d, *J* = 47.1 Hz), 7.07 – 7.17 (2H, m), 7.20 - 7.28 (1H, m), 7.39 - 7.49 (1H, m), 8.39 - 8.42 (1H, m), 11.47 - 12.06 (1H, m). MS $^m/_z$: 507 (M+1).

Ejemplo 224

Etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-fluorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 23 mg (45%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.1 Hz), 1.56 - 1.70 (2H, m), 1.78 - 1.89 (2H, m), 2.52 - 2.56 (1H, m), 3.14 - 3.24 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.51 - 4.63 (4H, m), 5.68 (2H, d, J = 47.1 Hz), 7.16 - 7.24 (2H, m), 7.27 - 7.34 (2H, m), 8.39 (1H, s). MS ^{m}/z: 507 (M+1).

Ejemplo 225

Etil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E´ de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(2-clorofenil)metanosulfonamida para producir etil 6-[4-({[(2-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato. Rendimiento: 24 mg (45%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 7.2 Hz), 1.56 - 1.74 (2H, m), 1.84 - 1.95 (2H, m), 2.56 - 2.66 (1H, m), 3.16 - 3.27 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.54 - 4.65 (2H, m), 4.80 (2H, s), 5.68 (2H, d, J = 47.3 Hz), 7.35-7.46 (3H, m), 7.48 - 7.55 (1H, m), 8.39 (1H, s). MS $^m/_z$: 523 (M+1).

Ejemplo 226

Etil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano -2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(3-clorofenil)metanosulfonamida para producir etil 6-[4-({[(3-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato.
Rendimiento: 24 mg (46%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.57 - 1.70 (2H, m), 1.76 - 1.88 (2H, m), 2.53 - 2.61 (1H, m), 3.15-3.27 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.55-4.63 (2H, m), 4.68 (2H, s), 5.68 (2H, d, J = 47.3 Hz), 7.18 - 7.52 (4H, m), 8.40 (1H, s). MS $^m/_z$: 523 (M+1).

Ejemplo 227

Etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-clorofenil)metanosulfonamida para producir etil 6-[4-({[(4-clorobencil) sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-(fluorometil)nicotinato.
Rendimiento: 24 mg (46%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.71 (2H, m), 1.80 - 1.90 (2H, m), 2.54 - 2.60 (1H, m), 3.13 - 3.26 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.55-4.63 (2H, m), 4.66 (2H, s), 5.68 (2H, d, J = 47.1 Hz), 7.30 (2H, d, J = 8.5 Hz), 7.46 (2H, d, J = 8.5 Hz), 8.38 - 8.41 (1H, m).
MS $^m/_z$: 523 (M+1).

Ejemplo 228

Etil 5-ciano-2-(fluorometil)-6-[4-({[(3-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(3-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(fluorometil)-6-

[4-({[(3-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato.
Rendimiento: 6 mg (12%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.1 Hz), 1.58 - 1.71 (2H, m), 1.79 - 1.88 (2H, m), 2.28 (3H, s), 2.52 - 2.58 (1H, m), 3.17 - 3.23 (2H, m), 4.25 (2H, q, J = 7.1 Hz), 4.48 4.68 (4H, m), 5.68 (2H, d, J = 47.1 Hz), 7.00 - 7.32 (4H, m), 8.40 (1H, s), 11.27 - 11.80 (1H, m). MS ^{m}/z: 503 (M+1).

Ejemplo 229

Etil 5-ciano-2-(fluorometil)-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil)piperidin-1-il]nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-metilfenil)metanosulfonamida para producir etil 5-ciano-2-(fluorometil)-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato.
Rendimiento: 20 mg (40%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.57 - 1.72 (2H, m), 1.80 - 1.92 (2H, m), 2.30 (3H, s), 2.54 - 2.64 (1H, m), 3.11 - 3.25 (2H, m), 4.26 (2H, q, J = 7.2 Hz), 4.52 4.68 (4H, m), 5.69 (2H, d, J = 47.3 Hz), 7.11 - 7.28 (4H, m), 8.41 (1H, s), 11.33 - 11.86 (1H, m). MS ^{m}/z: 503 (M+1).

Ejemplo 230

Etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-(fluorometil)nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(2,4-diclorofenil)metanosulfonamida para producir etil 5-ciano-6-[4-({[(2,4-diclorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-(fluorometil) nicotinato. Rendimiento: 21 mg (38%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30 (3H, t, J = 7.2 Hz), 1.56 - 1.72 (2H, m), 1.83 - 1.94 (2H, m), 2.54 - 2.59 (1H, m), 3.15-3.27 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.53 - 4.63 (2H, m), 4.73 (2H, s), 5.68 (2H, d, J = 47.3 Hz), 7.39 - 7.53 (2H, m), 7.62 - 7.70 (1H, m), 8.35 - 8.43 (1H, m). MS $^m/_z$: 557 (M+1).

Ejemplo 231

Etil 5-ciano-2-(fluorometil)-6-{4-[({[(4-metilciclohexil)metil]sulfonil} amino)carbonil]piperidin-1-il}nicotinato

Preparado de acuerdo con el método E' de ácido 1-[3-ciano-5-(etoxicarbonil)-6-(fluorometil)piridin-2-il]piperidin-4-carboxílico y 1-(4-metilciclohexil)metanosulfonamida para producir etil 5-ciano-2-(fluorometil)-6-{4-[({[(4-metilciclohexil)metil]sulfonil}amino)carbonil] piperidin-1-il}nicotinato.
Rendimiento: 18 mg (36%).
^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 - 0.90 (4H, m), 0.96 - 1.20 (3H, m), 1.29 (3H, t, J = 7.2 Hz), 1.38 - 1.69 (7H, m), 1.77 - 1.97 (3H, m), 1.99 - 2.09 (1H, m), 2.59 - 2.71 (2H, m), 3.16 - 3.29 (2H, m), 4.25 (2H, q, J = 7.2 Hz), 4.51 - 4.66 (2H, m), 5.67 (2H, d, J = 47.3 Hz), 8.39 (1H, s). MS ^{m}/z: 509 (M+1).

Ejemplo 232

Etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato

(a) *terc*-Butil 3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-carboxilato

DIPEA (0.3 mL, 1.72 mmol) se agregó a una mezcla de ácido [1-(*terc*-butoxicarbonil)azetidin-3-il]acético (193mg, 0.90 mmol) y TBTU (326mg, 1.02 mmol) en DCM seco (4mL). La mezcla de reacción se agitó a

temperatura de la sala durante 1 hora y se agregó 1-fenilmetanosulfonamida (169mg, 0.99 mmol) y la agitación se continuó a temperatura de la sala durante 19 horas. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con EtOAc (3 veces). La capa orgánica combinada se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó para producir *terc*-butil 3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-carboxilato, el cual se utilizó en el siguiente paso sin purificación adicional. Rendimiento: 383mg (116%). MS $^m/_z$: 367 (M-1).

(b) 2-Azetidin-3 -il-*N*-(bencilsulfonil)acetamida

El *terc*-butil 3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-carboxilato crudo del paso anterior (383mg, 0.90 mmol) se disolvió en DCM (5mL) y se agregó TFA (4mL). La mezcla de reacción se agitó a temperatura de la sala durante 1.5 horas. El disolvente se evaporó para producir 2-azetidin-3-il-N-(bencilsulfonil)acetamida, la cual se utilizó en el siguiente paso sin purificación adicional. Rendimiento: 240 mg (100%). MS ^{m}/z: 269 (M+1), 267 (M-1).

(c) Etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato

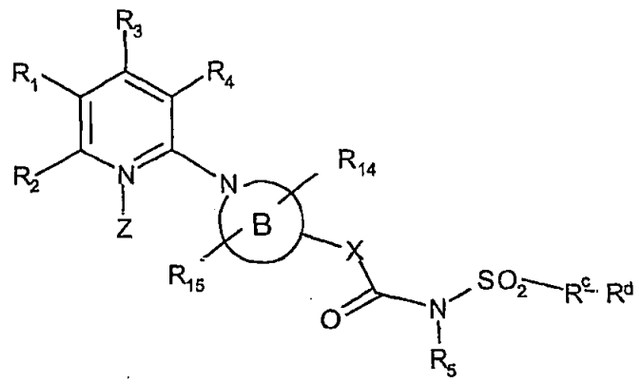
DIPEA (1 mL) se agregó a una solución de la 2-azetidin-3-il-N-(bencilsulfonil)acetamida cruda del paso anterior y etil 6-cloro-5-ciano-2-(difluorometil)nicotinato (180mg, 0.69 mmol) en EtOH (9mL). La mezcla de reacción se calentó a 120°C durante 5 minutos empleando calentamiento en microondas de nodo simple. Se agregó $NaHCO_3$ (acuoso) y la mezcla se extrajo con DCM (3 veces). La capa orgánica combinada se corrió a través de un separador de fase y se evaporó. El producto crudo se purificó mediante HPLC (Kromasil C8 10µm, 21.5x250mm empleando una gradiente de CH_3CN /0.1 M NH_4OAc 20% a 50%, caudal 25 mL/minuto)

para producir etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-(difluorometil)nicotinato. Rendimiento: 156mg (46% en 3 pasos). ^{1}H NMR (500MHz, DMSO-d_6): δ 1.31 (3H, t, *J* =7.1Hz), 2.71 (2H, d, *J* =7.6Hz), 3.04-3.11(1H, m). 4.08 (2H, aparente br s), 4.28 (2H, q, *J* =7.1Hz), 4.52 (2H, br s aparente), 4.70 (2H, s), 7.29-7.32 (2H, m), 7.37-7.44 (3H, m), 7.40 (1H, t, *J* =53Hz, -CHF2), 8.44 (1H, s), 11.68 (1H, s).
MS $^m/_z$: 493 (M+1), 491(M-1).

223

REIVINDICACIONES

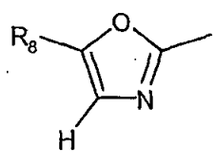
1. Un compuesto de fórmula I o su sal farmacéuticamente aceptable:



(I)

en donde

R_1 representa $R_6OC(O)$, $R_7C(O)$, $R_{16}SC(O)$, $R_{17}S$, $R_{18}C(S)$ o un grupo gH



(gII),

R_2 representa H, CN, halógeno (F, Cl, Br, I), NO_2, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_{12})alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil (C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(2)}R^{b(2)}$

en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Además, R_1 + R_2 juntos (con dos átomos de carbono del anillo piperidina) pueden formar una lactona cíclica de 5 ó 6 miembros;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_3 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)Cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(3)}R^{b(3)}$ en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, COOH, (C_1-C_6)alcoxicarbonilo, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_4 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alquilcicloalquilo, (C_1-C_{12})alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I),

OH y/o COOH y/o (C_1-C_6)alcoxicarbonilo; además R_4 representa (C_1-C_{12})alquiltioC(O), (C_1-C_{12})alquilC(S), (C_1-C_{12})alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_{12})alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_{12})alquilC(O), (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(4)}R^{b(4)}$ en la cual $R^{a(4)}$ y $R^{b(4)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(4)}$ y $R^{b(4)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Z representa O o está ausente;

R_5 representa H o (C_1-C_{12})alquilo;

R_6 representa (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno, (con la salvedad que cualquier oxígeno tal tiene que estar por lo menos 2 átomos de carbono alejado del éster-oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_6 representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_{12})alquilo, arilo o heterociclilo;

R_7 representa (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I), además R_7 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, arilo o heterociclilo;

R_8 representa H, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o

uno o más átomos de halógeno (F, Cl, Br, I); además R_8 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo;

R_{14} representa H, OH con la salvedad que el grupo OH tiene que estar por lo menos 2 átomos de carbono alejado de cualquier heteroátomo en el anillo B/sistema de anillo, (C_1-C_{12})alquilo, interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más de OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_{12})alquilo sustituido opcionalmente por uno o más de átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_12)alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo, un grupo de fórmula $NR^{a(14)}R^{b(14)}$ en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O), (C_1-C_{12})alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo

en el sistema de anillo/anillo B, (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_{12})alquil sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{15} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(15)}R^{b(15)}$, en la cual $R^{a(15)}$ y $R^{b(15)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O)), (C_1-C_{12})alcoxiC(O) o $R^{a(15)}$ y $R^{b(15)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{16} representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{16} representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{17} representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{17} representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{18} representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo,

heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{18} representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_{12})alquilo, (C_1-C_{12})alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido o polisustituido, un grupo (C_1-C_4)oxoalquileno, un grupo (C_1-C_4)alquilenoxi o un grupo oxi-(C_1-C_4)alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido, (C_1-C_4)alquilenimino o (C_1-C_4)alquilenimino (-N(R_{19})-((C_1-C_4)alquileno) N-sustituido, en donde los mencionados grupos alquileno son no sustituidos, o monosustituidos o polisustituidos con cualesquiera sustituyentes de acuerdo con lo anterior;

R_{19} representa H o (C_1-C_4)alquilo;

R^d representa (C_3-C_8)cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, (C_1-C_{12})alquilo, (C_1-C_{12})alcoxiC(O), (C_1-C_{12})alcoxi, (C_1-C_{12})alquilo halógeno sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_{12})alquilsulfinilo, (C_1-C_{12})alquilsulfonilo, (C_1-C_{12})alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_{12})alquiltio, aril(C_1-C_{12})alquilsulfinilo, aril(C_1-C_{12})alquilsulfonilo, heterociclil(C_1-C_{12})alquiltio, heterociclil(C_1-C_{12})alquilsulfinilo, heterociclil(C_1-C_{12})alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquiltio, (C_3-

C_6)cicloalquil(C_1-C_{12})alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_{12})alquilsulfonilo o un grupo de fórmula $NR^{a(Rd)}R^{b(Rd)}$, en la cual $R^{a(Rd)}$ y $R^{b(Rd)}$ representan independientemente H, (C_1-C_{12})alquilo, (C_1-C_{12})alquilC(O) o $R^{a(Rd)}$ y $R^{b(Rd)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

X representa un enlace simple, imino (-NH-), metileno (-CH_2-), iminometileno (-CH_2-NH-) en donde el carbono se conecta al anillo B/sistema de anillo, metilenimino (-NH-CH_2-) en donde el nitrógeno se conecta al anillo B/sistema de anillo y cualquier carbono y/o nitrógeno en estos grupos puede sustituirse opcionalmente con (C_1-C_6) alquilo; además X puede representar un grupo (-CH_2-)n en donde n= 2-6, que opcionalmente es insaturado y/o se sustituye por uno o más sustituyentes seleccionados entre halógeno, hidroxilo o (C_1-C_6)alquilo; y

B es un anillo/sistema de anillo de 4 a 11 miembros, monocíclico o bicíclico, que comprende uno o más átomos de nitrógeno y, opcionalmente, uno o más átomos seleccionados de oxígeno o azufre, el cual nitrógeno se conecta al anillo piridina (de acuerdo con fórmula I) y, además, el anillo B/sistema de anillo se conecta a X en otra de sus posiciones. Los sustituyentes R_{14} y R_{15} se conectan al anillo B/sistema de anillo de tal manera que no se forman compuestos de amonio cuaternario (mediante estas conexiones).

2. Un compuesto de acuerdo con la reivindicación 1 en donde

R_2 representa H, CN, NO_2, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi,

arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(2)}R^{b(2)}$, en la cual $Ra^{(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

Además, R_1 + R_2 juntos (con dos carbonos del anillo piridina) pueden formar una lactona cíclica de 5 miembros o 6 miembros;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_3 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_3 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(3)}R^{b(3)}$, en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o

$R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, COOH, (C_1-C_6)alcoxicarbonilo, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_4 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH y/o COOH y/o (C_1-C_3)alcoxicarbonilo; además R_4 representa (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(4)}R^{b(4)}$, en la cual $R^{a(4)}$ y $R^{b(4)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(4)}$ y $R^{b(4)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_5 representa H o (C_1-C_6)alquilo;

R_6 representa (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, (con la condición que cualquier oxígeno tiene que estar alejado por lo menos 1 átomo de carbono del éster-oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_6 representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_6)alquilo, arilo o heterociclilo;

R_7 representa (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_7 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, arilo o heterociclilo;

R_8 representa H, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_8 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo;

R_{14} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_6)alquilsurfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-

C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(14)}R^{b(14)}$, en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{15} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo, (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo o un grupo de fórmula $NR^{a(15)}R^{b(15)}$, en la cual $R^{a(15)}$ y $R^{b(15)}$ representan independientemente H, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(15)}$ y $R^{b(15)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

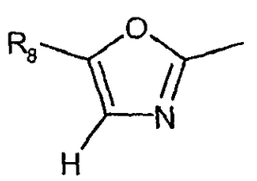
R_{16} representa (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{16} representa (C_3-C_6)cicloalquilo, hidroxi(C_2-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, o heterociclilo;

R_{17} representa $(C_1\text{-}C_6)$alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_{17} representa $(C_3\text{-}C_6)$cicloalquilo, hidroxil$(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalcoxi, arilo o heterociclilo;

R_{18} representa $(C_1\text{-}C_6)$alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I): además R_{18} representa $(C_3\text{-}C_6)$cicloalquilo, hidroxi$(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$alcoxi, $(C_3\text{-}C_6)$cicloalcoxi, arilo o heterociclilo; y

R^d representa $(C_3\text{-}C_8)$cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, OH, CN, NO_2, $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$alcoxiC(O), $(C_1\text{-}C_6)$alcoxi, $(C_1\text{-}C_6)$alquilo halógeno sustituido, $(C_3\text{-}C_6)$cicloalquilo, arilo, heterociclilo, $(C_1\text{-}C_6)$alquilsulfonilo, $(C_1\text{-}C_6)$alquiltio, $(C_3\text{-}C_6)$cicloalquiltio, arilsulfinilo, arilsulfonilo, ariltio, aril$(C_1\text{-}C_6)$alquiltio, aril$(C_1\text{-}C_6)$alquilsulfinilo, aril$(C_1\text{-}C_6)$alquilsulfonilo, heterociclil$(C_1\text{-}C_6)$alquilsulfonilo o un grupo de fórmula $NR^{a(Rd)}R^{b(Rd)}$, en la cual $R^{a(Rd)}$ y $R^{b(Rd)}$ representan independientemente H, $(C_1\text{-}C_6)$alquilo, $(C_1\text{-}C_6)$alquilC(O) o $R^{a(Rd)}$ y $R^{b(Rd)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina.

3. Un compuesto de acuerdo con la reivindicación 2 en donde;
R_1 representa $R_5OC(O)$, $R_{16}SC(O)$, o un grupo gII,



(gII);

R_2 representa H, CN, NO_2, $(C_1\text{-}C_6)$alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo,

cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), o un grupo de fórmula $NR^{a(2)}R^{b(2)}$, en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_3 representa H, CN, NO_2, halógeno (F, Cl, Br, I), (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_3 representa (C_1-C_6)alcoxi sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I); además R_3 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O), aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), (C_1-C_6)alquilsulfinilo, o un grupo de fórmula $NR^{a(3)}R^{b(3)}$, en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_6)alqúilo, (C_1-C_6)alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa H, CN, NO_2, halógeno (F, Cl, Br, I), opcionalmente interrumpido por oxígeno y/o sustituido opcionalmente por OH, COOH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno; además R_4 representa (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxi, en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH y/o COOH y/o metoxicarbonilo; además R_4 representa (C_1-C_6)alquiltioC(O), (C_1-C_6)alquilC(S), (C_1-C_6)alcoxiC(O), (C_3-C_6)cicloalcoxi, arilo, arilC(O),

aril(C_1-C_6)alquilC(O), heterociclilo, heterociclilC(O), heterociclil(C_1-C_6)alquilC(O), o un grupo de fórmula $NR^{a(4)}R^{b(4)}$ en la cual $R^{a(4)}$ y $R^{b(4)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(4)}$ y $R^{b(4)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_8 representa H, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_8 representa (C_3-C_6)cicloalquilo, hidroxiC_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo o heterociclilo;

R_{14} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo o un grupo de fórmula $NR^{a(14)}R^{b(14)}$, en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O), o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F,

Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{15} representa arilo, heterociclilo, uno o más átomos de halógeno (F, Cl, Br, I), (C_3-C_6)cicloalquilo, hidroxi(C_1-C_6)alquilo,(C_1-C_6)alcoxi, (C_3-C_6)cicloalcoxi, arilo, heterociclilo o un grupo de fórmula $NR^{a(15)}R^{b(15)}$ en la cual $R^{a(15)}$ y $R^{b(15)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O), o $R^{a(15)}$ y $R^{b(15)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{16} es etilo;

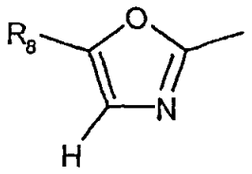
R^c representa un grupo(C_1-C_4)alquileno no sustituido o monosustituido o polisustituido, un grupo (C_1-C_4)oxoalquileno, un grupo (C_1-C_4)alquilenoxi o un grupo oxi-(C_1-C_4)alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo, (C_1-C_4)alcoxilo, oxi-(C_1-C_4)alquilo, (C_2-C_4)alquenilo, (C_2-C_4)alquinilo, (C_3-C_6)cicloalquilo, carboxilo, carboxi-(C_1-C_4)alquilo, arilo, heterociclilo, nitro, ciano, halógeno (F, Cl, Br, I), hidroxilo, $NR^{a(Rc)}R^{b(Rc)}$ en la cual $R^{a(Rc)}$ y $R^{b(Rc)}$ individual e independientemente de cada uno representan hidrógeno, (C_1-C_4)alquilo o $R^{a(Rc)}$ y $R^{b(Rc)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido, (C_1-C_4)alquilenimino o (C_1-C_4)alquilenimino (-N(R_{19})-((C_1-C_4)alquileno) N-sustituido en donde los mencionados grupos alquileno son no sustituidos, o monosustituidos o polisustituidos con cualesquiera sustituyentes de acuerdo con lo anterior; y

R^d representa (C_3-C_8)cicloalquilo, arilo o heterociclilo, y uno cualquiera de estos grupos sustituido opcionalmente con uno o más átomos de halógeno (F, Cl, Br, I) y/o uno o más de los siguientes grupos, CN, NO_2, (C_1-C_6)alquilo, (C_1-C_6)alcoxi, (C_1-C_6)alquilo halo sustituido, (C_3-C_6)cicloalquilo, arilo, heterociclilo, (C_1-C_6)alquilsulfinilo, (C_1-C_6)alquilsulfonilo, (C_1-C_6)alquiltio, (C_3-C_6)cicloalquiltio, arilsulfinilo,

arilsulfonilo, ariltio, aril(C_1-C_6)alquiltio, aril(C_1-C_6)alquilsulfinilo, aril(C_1-C_6)alquilsulfonilo, heterociclil(C_1-C_6)alquiltio, heterociclil(C_1-C_6)alquilsulfinilo, heterociclil(C_1-C_6)alquilsulfonilo, (C_3-C_6)cicloalquil(C_1-C_6)alquiltio, (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfinilo o (C_3-C_6)cicloalquil(C_1-C_6)alquilsulfonilo.

4. Un compuesto de acuerdo con la reivindicación 1 en donde;

R^1 representa $R_6OC(O)$, $R_{16}SC(O)$ o un grupo gII



(gII);

R_2 representa H o (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_2 representa un grupo de fórmula $NR^{a(2)}R^{b(2)}$, en la cual $R^{a(2)}$ y $R^{b(2)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(2)}$ y $R^{b(2)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_3 representa H o un grupo de fórmula $NR^{a(3)}R^{b(3)}$, en la cual $R^{a(3)}$ y $R^{b(3)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O) o $R^{a(3)}$ y $R^{b(3)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_4 representa CN, halógeno (F, Cl, Br, I), además R_4 representa (C_1-C_6)alquilC(O), (C_1-C_6)alcoxi en donde el grupo alcoxi puede sustituirse opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH y/o COOH y/o metoxicarbonilo;

R_5 representa H;

R_6 representa (C_1-C_{12})alquilo interrumpido opcionalmente por oxígeno, (con la condición que tal oxígeno tiene que estar alejado por lo menos 2 átomos de carbono del éster oxígeno que conecta el grupo R_6) y/o sustituido opcionalmente por OH, arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I); además R_5 representa (C_3-C_6)cicloalquilo o hidroxi(C_2-C_{12})alquilo;

R_8 representa H, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno, y/o sustituido opcionalmente por arilo, cicloalquilo, heterociclilo o uno o más átomos de halógeno (F, Cl, Br, I);

R_{14} representa H, OH con la condición que el grupo OH tiene que estar alejado por lo menos 2 átomos de carbono de cualquier heteroátomo en el sistema de anillo/anillo B, (C_1-C_6)alquilo interrumpido opcionalmente por oxígeno y/o sustituido opcionalmente por uno o más OH, COOH y $COOR^e$; en donde R^e representa arilo, cicloalquilo, heterociclilo o (C_1-C_6)alquilo sustituido opcionalmente por uno o más átomos de halógeno (F, Cl, Br, I), OH, arilo, cicloalquilo y heterociclilo; además R_{14} representa o un grupo de fórmula $NR^{a(14)}R^{b(14)}$, en la cual $R^{a(14)}$ y $R^{b(14)}$ representan independientemente H, (C_1-C_6)alquilo, (C_1-C_6)alquilC(O), (C_1-C_6)alcoxiC(O) o $R^{a(14)}$ y $R^{b(14)}$ junto con el átomo de nitrógeno representan piperidina, pirrolidina, azetidina o aziridina;

R_{15} representa H;

R_{16} es etilo;

R^c representa un grupo (C_1-C_4)alquileno no sustituido o monosustituido, un grupo (C_1-C_4)alquilenoxi o un grupo oxi-(C_1-C4)alquileno, en donde cualesquiera sustituyentes, cada uno individual e independientemente, se seleccionan de (C_1-C_4)alquilo; además R^c representa imino (-NH-), imino (-NR_{19}-) N-sustituido;

R_{14} se selecciona de un grupo conformado por H, metilo, *terc*-butiloxicarbonil-imino y amino;

R_{15} es H;

R_{16} es etilo;

R^c se selecciona de un grupo conformado por metileno (-CH_2-), metilmetileno (-$CH(CH_3)$-), etileno (-CH_2CH_2-), oxipropileno (-$OCH_2CH_2CH_2$-), imino (-NH-) y metilimino (-$N(CH_3)$-;

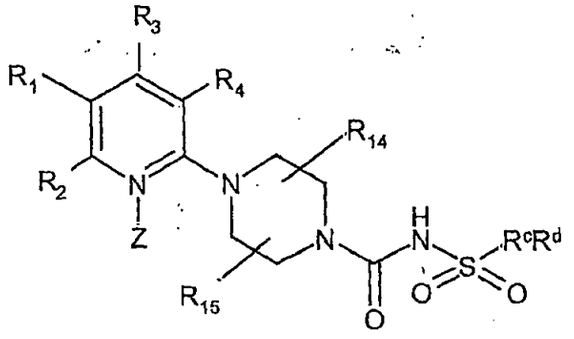
R_{19} se selecciona de un grupo conformado por H y metilo;

R^d se selecciona de un grupo conformado por ciclopentilo, ciclohexilo, 4-metilciclohexilo, fenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 4-etilfenilo, 2-metoxicarbonil-fenilo, 3-(trifluorometil)fenilo, 4-(trifluorometil)fenilo, 2-(trifluorometil)fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 2-clorofenilo, 3-clorofenilo, 4-clorofenilo, 3-bromofenilo, 4-cianofenilo, 4-metoxifenilo, 2-nitrofenilo, 3-nitrofenilo, 4-nitrofenilo, 3,4-diclorofenilo, 3,5-diclorofenilo, 3,4-difluorofenilo, 2,5-dimetilfenilo, 3,5-dimetilfenilo, 4-isopropilfenilo, 3-fluoro-4-metil-fenilo, 2-piridilo, 3-piridilo, 4-piridilo, N-óxido-2-piridilo, 6-[3-benzo[d]isoxazol-3-ilo] y N-[(1,2-benzisoxazol-3-ilo)];

X representa un enlace simple, imino (-NH-) o metileno (-CH_2-); y

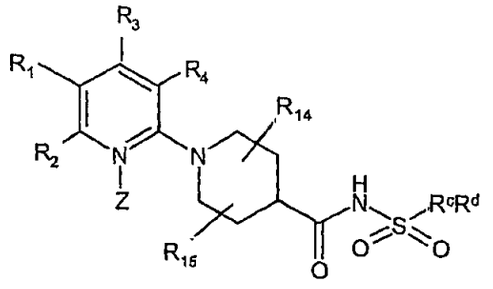
B se selecciona del grupo conformado por 4-piperazin-1-ileno, 4-piperidin-1-ileno, 3-piperidin-1-ileno, 3-azetidin-1-ileno, y los sustituyentes R_{14} y R_{15} se conectan al sistema de anillo/anillo B, de tal modo que no se formen compuestos de amonio cuaternario (mediante estas conexiones).

6. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (Ia):



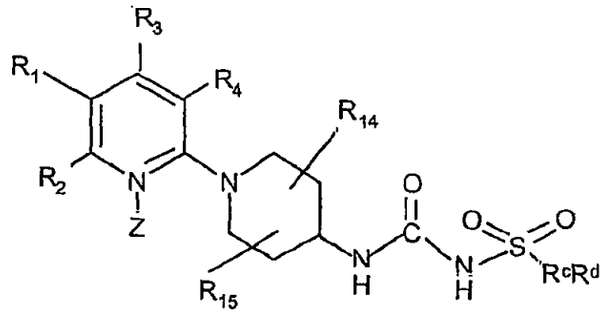
(Ia)

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (Ib):



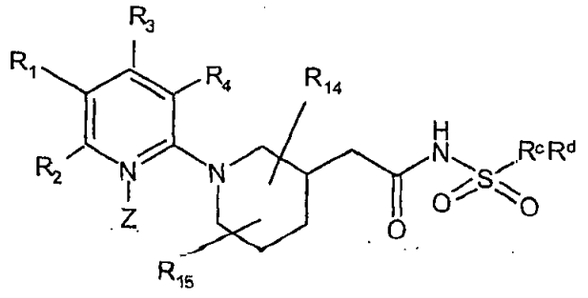
(Ib)

8. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (Ic):



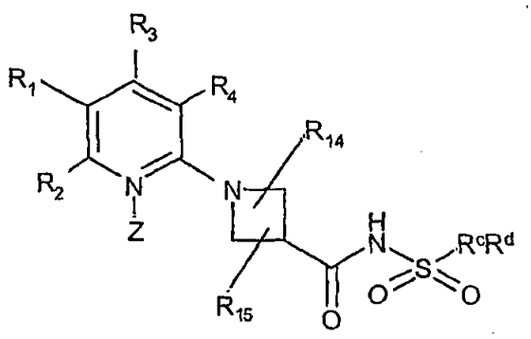
(Ic)

9. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (Id):



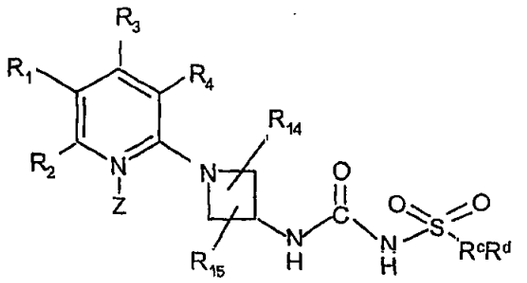
(Id)

10. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (Ie):



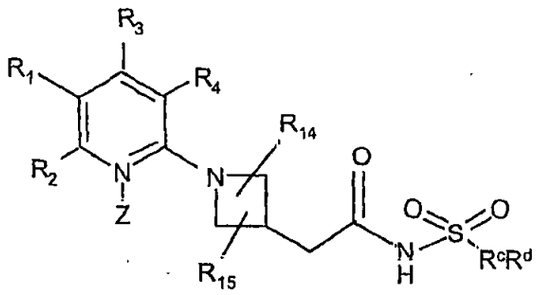
(Ie)

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (If):



(If)

12. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 que es de la fórmula (Ig):



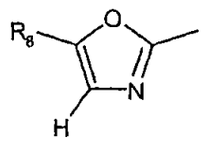
(Ig)

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-12 en donde Z está ausente.

14. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-12 en donde Z es O.

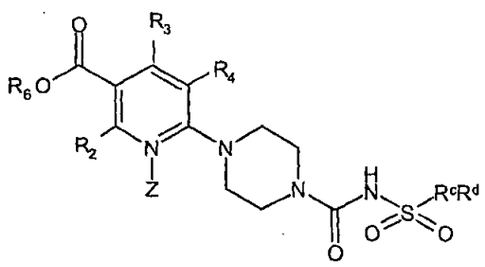
15. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 en donde R_1 representa $R_6OC(O)$.

16. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 en donde R_1 representa $R_{16}SC(O)$ o un grupo gII



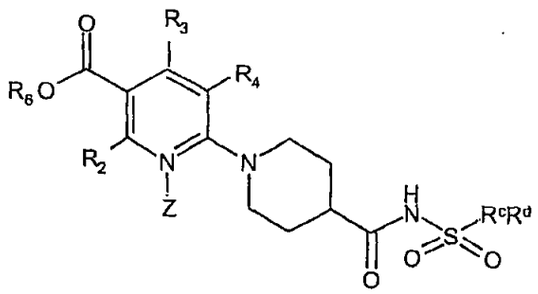
(gII).

17. Un compuesto de acuerdo con la reivindicación 15 que es de la fórmula (Iaa):



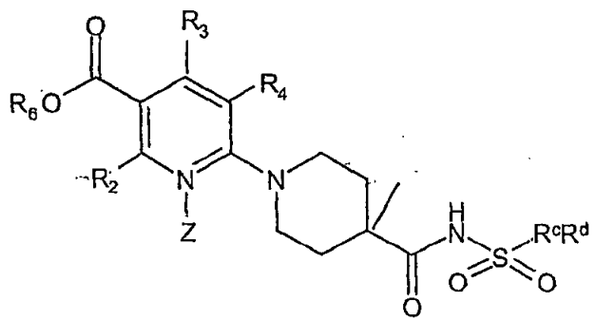
(Iaa).

18. Un compuesto de acuerdo con la reivindicación 15 que es de la fórmula (Ibb):



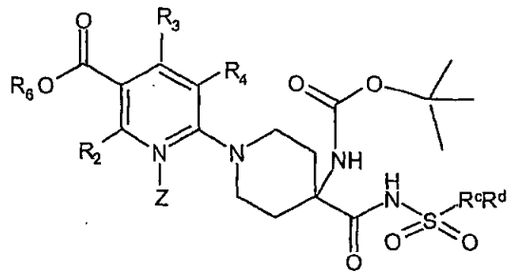
(Ibb).

19. Un compuesto de acuerdo con la reivindicación 15 que es de la fórmula (Ibc):



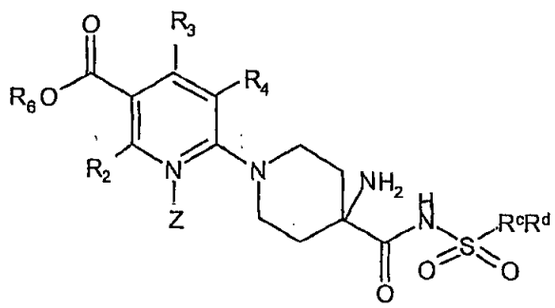
(Ibc).

20. Un compuesto de acuerdo con la reivindicación 15 que es de la fórmula (Ibd):



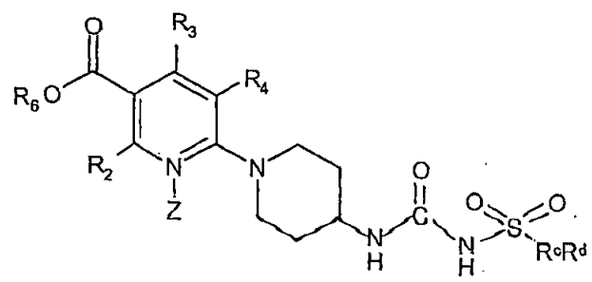
(Ibd).

21. Un compuesto de acuerdo con la reivindicación15 que es de la fórmula (Ibe):



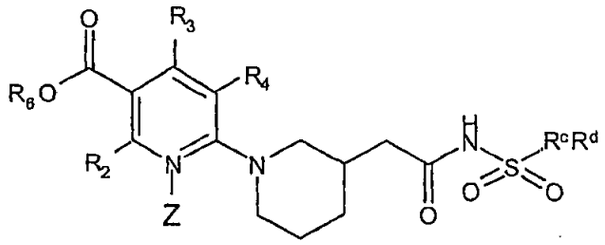
(Ibe).

22. Un compuesto de acuerdo con la reivindicación 15 que es de la fórmula (Ice):



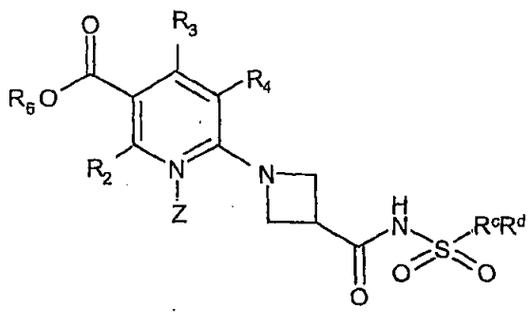
(Icc).

23. Un compuesto de acuerdo con la reivindicación 15 que es de la fórmula (Idd):



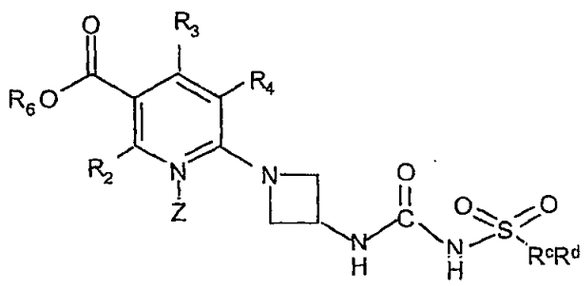
(Idd).

24. Un compuesto de acuerdo con la reivindicaciónl5 que es de la fórmula (Iee):



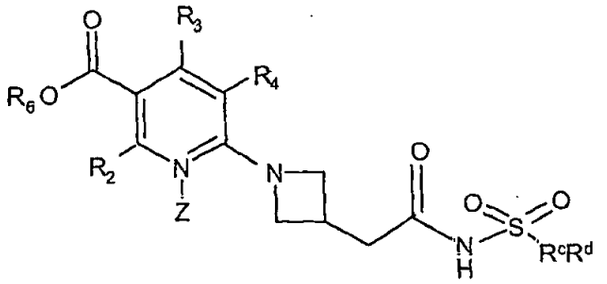
(Iee).

25. Un compuesto de acuerdo con la reivindicaciónl5 que es de la fórmula (Iff):



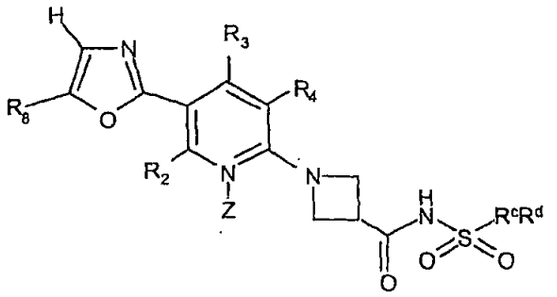
(Iff).

26. Un compuesto de acuerdo con la reivindicación 16 que es de la fórmula (Igg):



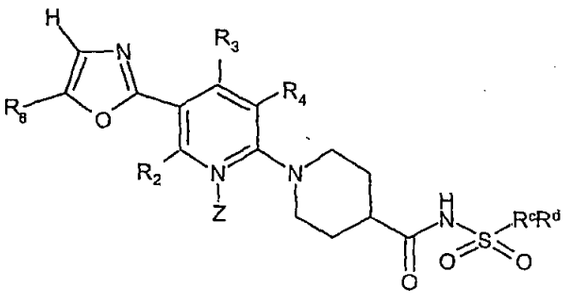
(Igg).

27. Un compuesto de acuerdo con la reivindicación 16 que es de la fórmula (Ihh):



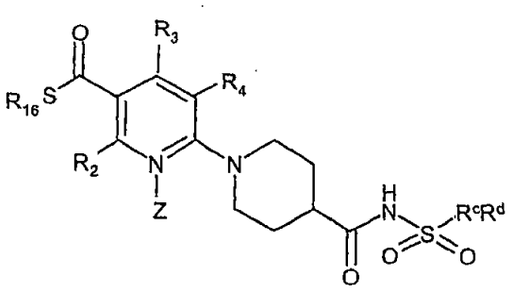
(Ihh).

28. Un compuesto de acuerdo con la reivindicación 16 que es de la fórmula (Iii):



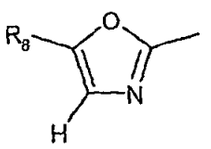
(Iii).

29. Un compuesto de acuerdo con la reivindicación 16 que es de la fórmula (Ijj):



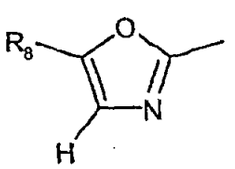
(Ijj).

30. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1-5 en donde R_1 representa $R_6OC(O)$, $R_{16}SC(O)$ o un grupo gII



(gII).

31. Un compuesto de acuerdo con la reivindicación 30 en donde R_1 representa un grupo gII;



(gII).

32. Un compuesto de acuerdo con la reivindicación 30 en donde R_1 representa $R_{16}SC(O)$.

33. Un compuesto seleccionado de:

etil éster de ácido 5-ciano-6-[3-(1-metoxicarbonil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;

etil éster de ácido 6-[3-({[(3-bromobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-metilnicotínico;

etil éster de ácido 5-ciano-2-metil-6-[3-(2-nitro-fenilmetanosulfonilaminocarbonil)-zetidin-1-il]-nicotínico;

etil éster de ácido 6-[3-(2-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;

etil éster de ácido 6-[3-(4-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil- nicotínico;

etil éster de ácido 5-ciano-2-metil-6-[3-(4-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;

etil éster de ácido 5-ciano-6-[3-(3-fluoro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;

etil éster de ácido 5-ciano-2-metil-6-[3-(3-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;

etil éster de ácido 6-[3-(3-cloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;
etil éster de ácido 6-{3-[2-(3-cloro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-5-ciano-2-metil-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(4-nitro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(2-fenil-etanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-(3-o-tolilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(3-nitro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-6-{3-[2-(4-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico;
etil éster de ácido 5-ciano-2-metil-6-[3-(2-trifluorometil-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-nicotínico;
etil éster de ácido 5-ciano-6-[3-(4-fluoro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-(3-ciclopentilmetanosulfonilaminocarbonil-azetidin-1-il)-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-{3-[2-(2-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-[3-(3,5-dicloro-fenilmetanosulfonilaminocarbonil)-azetidin-1-il]-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-(3-ciclohexilmetanosulfonilaminocarbonil-azetidin-1-il)-2-metil-nicotínico;
etil éster de ácido 5-ciano-6-{3-[2-(3-fluoro-fenil)-etanosulfonilaminocarbonil]-azetidin-1-il}-2-metil-nicotínico;
etil éster de ácido 6-[3-(benzo[d]isoxazol-3-ilmetanosulfonilaminocarbonil)-azetidin-1-il]-5-ciano-2-metil-nicotínico;
1-[4-amino-3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il]-*N*-(bencilsulfonil) piperidin-4-carboxamida;

etil éster de ácido 4-amino-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloronicotínico;

isopropil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicotínico;

terc-butil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino) azetidin-1-il]-5-ciano-2-metilnicotínico;

etil éster de ácido 6-[3-({[(bencilsulfonil)amino]carbonil}amino)azetidin-1-il]-5-ciano-2-metilnicotínico;

etil éster de ácido 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}piperidin-1-il)-5-ciano-2-metilnicotínico;

etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}-4-metilpiperidin-1-il)-5-ciano-2-metilnicotínico;

N-(bencilsulfonil)-1-[3-cloro-5-(5-etil-1,3-oxazol-2-il)piridin-2-il] piperidin-4-carboxamida;

ciclopentil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico;

propil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico;

etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-isopropilnicotínico;

etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-etilnicotínico;

2,2-dimetilpropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico;

N-(bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida;

isopropil éster de ácido 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotínico;

isopropil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico;

etil éster de ácido 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotínico;

etil éster de ácido 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotínico;

etil éster de ácido 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotínico;

N-[(1,2-benzisoxazol-3-ilmetil)sulfonil]-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida;

N-(bencilsulfonil)-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]azetidin-3-carboxamida;

N-[(4-clorobencil)sulfonil]-1-[3-ciano-5-(5-etil-1,3-oxazol-2-il)-6-metilpiridin-2-il]piperidin-4-carboxamida;

etil éster de ácido 5-ciano-2-metil-6-(3-fenilmetanosulfonilaminocarbonil-azetidin-1-il)-nicotínico;

etil 5-ciano-6-{3-[({[3-(4-metoxifenoxi)propil]sulfonil}amino)carbonil] azetidin-1-il}-2-metilnicotinato;

etil 4-amino-6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloronicotinato;

etil 5-ciano-2-metil-6-[3-({[(3-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

2,2-dimetilpropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 6-[4-({[(3-bromobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato;

ciclopropil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

2,2,2-trifluoroetil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)- 5-ciano-2-metilnicotinato;

2,2,2-trifluoroetil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)- 5-ciano-2-metilnicotinato;

2,2,2-trifluoroetil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]-5-ciano-2-metilnicotinato;

ciclopropil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

ciclobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

2-hidroxietil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

bencil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(3,4-diclorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(3,4-diclorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(4-cianobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-isopropilnicotinato;

etil 6-(3-{[bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-etilnicotinato;

etil 5-ciano-2-metil-6-[3-({[(1-feniletil)sulfonil]amino}carbonil)azetidin-1-il]nicotinato;

propil 6-(3-{[(bencilsulfonil)amino]carbonil)azetidin-1-il)-5-ciano-2-metilnicotinato;

isobutil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-metilnicotinato;

isopropil 5-ciano-2-metil-6-{4-[({[4-(trifluorometil)bencil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato;

isopropil 5-ciano-2-metil- 6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

isopropil 5-ciano-2-metil-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

isopropil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(2-fluorobencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

isopropil 6-[4-({[(3-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilnicotinato;

isopropil 6-[4-({[(2-clorobencil)sulfonil]amino}carbonil)piperidin-1-il] -5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-6-{4-[({[2-(metoxicarbonil)bencil]sulfonil}amino)carbonil] piperidin-1-il}-2-metilnicotinato;

etil 5-ciano-6-[4-({[(3-fluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-2-metil-6-{4-[({[2-(2-metilfenil)etil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato;

ácido 4-{[2-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(4-metoxi-4-oxobutoxi)-2-metilnicotinato;

etil 6-(4-{[(anilinosulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-{4-[({[metil(fenil)amino]sulfonil}amino)carbonil] piperidin-1-il}nicotinato;

isopropil 5-ciano-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

isopropil 5-ciano-6-[3-({[(3-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-2-metil-6-[3-({[(2-feniletil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

isopropil 5-ciano-6-[3-({[(ciclopentilmetil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-{3-[({[2-(metoxicarbonil)bencil]sulfonil}amino) carbonil] azetidin-1-il}-2-metilnicotinato;

isopropil 5-ciano-6-[3-({[(2-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 6-[3-({[(4-clorobencil)sulfonil]amino}carbonil)azetidin-1-il]- 5-ciano-2-metilnicotinato;

isopropil 5-ciano-6-[3-({[(4-fluorobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[3-({[(4-cianobencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

metil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

metil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

S-etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilpiridin-3-carbotioato;

S-etil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino} carbonil) piperidin-1-il]piridin-3-carbotioato;

S-etil 6-[4-({[(4-clorobencil)sulfonil]amino}carbonil)piperidin-1-il]-5-ciano-2-metilpiridin-3-carbotioato;

S-etil 5-ciano-6-[4-({[(4-fluorobencil)sulfonil]amino} carbonil)piperidin-1-il]-2-metilpiridin-3-carbotioato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-metoxi-2-metilnicotinato;

etil 6-[4-({[(bencilsulfonil)amino]carbonil}amino)piperidin-1-il]-5-ciano-2-metilnicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperazin-1-il)-5-ciano-2-metilnicotinato;

ácido 4-{[2-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-(etoxicarbonil)-6-metilpiridin-3-il]oxi}butanoico;

etil 5-ciano-2-metil-6-{3-[({[(1-oxidopiridin-2-il)metil]sulfonil}amino) carbonil]azetidin-1-il}nicotinato;

etil 5-ciano-2-metil-6-[3-({[(piridin-3-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-{4-[({[(1-oxidopiridin-2-il)metil]sulfonil}amino) carbonil]piperidin-1-il}nicotinato;

etil 5-ciano-2-metil-6-[4-({[(piridin-3-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-(dimetilamino)nicotinato;

etil 5-ciano-2-metil-6-[4-({[(piridin-4-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-[3-({[(piridin-2-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(3,5-dimetilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;

isopropil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(2,5-dimetilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(4-isopropilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

bencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-2-metil-6-{4-[({[(4-metilciclohexil)metil]sulfonil}amino) carbonil] piperidin-1-il}nicotinato;

etil 5-ciano-6-[3-({[(4-isopropilbencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-2-metil-6-[4-({[(2-feniletil)sulfonil]amino}carbonil)piperidin-1-il]nicotinato;

etil 5-ciano-2-metil-6-[4-({[(piridin-2-ilmetil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

etil 5-ciano-6-[3-({[(2,5-dimetilbencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato;

etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-cloro-2-metilnicotinato;

etil 6-(3-{2-[(bencilsulfonil)amino]-2-oxoetil}azetidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-6-[4-({[(ciclopentilmetil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-(2-{[(4-fluorobencil)sulfonil]amino}-2-oxoetil)azetidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[4-({[(3-fluoro-4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]-2-metilnicotinato;

etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-cloro-2-metilnicotinato;

4-fluorobencil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;

etil 5-ciano-6-[4-({[(4-etilbencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-6-[3-({[(3,4-difluorobencil)sulfonil]amino}carbonil) azetidin-1-il]-2-metilnicotinato;

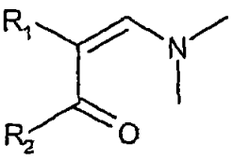
etil 5-ciano-6-[4-({[(4-metoxibencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;

etil 5-ciano-2-metil-6-[4-({[(3-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;

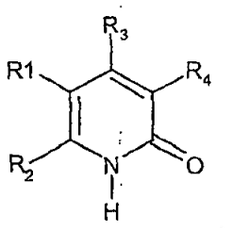
etil 5-ciano-6-[3-({[(4-etilbencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;
etil 5-cloro-2-metil-6-[3-({[(4-metilbencil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;
etil 5-ciano-6-[4-({[(3,4-difluorobencil)sulfonil]amino}carbonil)piperidin-1-il]-2-metilnicotinato;
etil 5-ciano-6-[3-({[(4-metoxibencil)sulfonil]amino}carbonil)azetidin-1-il]-2-metilnicotinato;
ciclopropil 5-ciano-2-metil-6-[4-({[(4-metilbencil)sulfonil]amino}carbonil) piperidin-1-il]nicotinato;
etil 5-ciano-2-metil-6-[3-({[(piridin-4-ilmetil)sulfonil]amino}carbonil) azetidin-1-il]nicotinato;
etil 6-(3-{[(bencilsulfonil)amino]carbonil}azetidin-1-il)-5-ciano-2-(dimetilamino)nicotinato;
1-óxido de etil 6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;
etil 5-acetil-6-(4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-2-metilnicotinato;
etil 6-{4-{[(bencilsulfonil)amino]carbonil}-4-[(terc-butoxicarbonil)amino] piperidin-1-il}-5-ciano-2-metilnicotinato
etil 6-(4-amino-4-{[(bencilsulfonil)amino]carbonil}piperidin-1-il)-5-ciano-2-metilnicotinato;
y sus sales farmacéuticamente aceptables.

34. Un proceso para fabricar un compuesto de fórmula (I), en la cual R_2, R_3, R_4, B, R_{14}, R_{15}, R^c y R^d se definen de acuerdo con una cualquiera de las reivindicaciones 1-5, R_1 es $R_6OC(O)$ en donde R_6 se define de acuerdo con una cualquiera de las reivindicaciones 1-5, X es un enlace simple, Z está ausente y R_5 es hidrógeno, caracterizado por que el proceso comprende los siguientes pasos (I-vi);

i.) Hacer reaccionar un compuesto de la fórmula $R_1CH_2C(O)R_2$, con dimetoxi-N,N-dimetilmetanoamina para formar un compuesto de la fórmula



ii.) Hacer reaccionar el compuesto del paso i) con un compuesto de la fórmula general $R_4CH_2C(O)NH_2$ en un disolvente inerte, tal como etanol, en la presencia de una base fuerte tal como etóxido de sodio, para producir un compuesto de la fórmula general



en la cual R_2, R_3, R_4, se definen de acuerdo con una cualquiera de las reivindicaciones 1-5, R_1 es $R_6OC(O)$ en donde R_6 se define de acuerdo con una cualquiera de las reivindicaciones 1-5, y Z está ausente.

iii) El producto del paso ii) se lava primero con una solución de agua alcalina, por ejemplo, una solución de bicarbonato de sodio y luego se lava con agua, luego de lo cual el producto lavado se recolecta.

iv.) El compuesto del paso iii) se hace reaccionar con un agente clorante, tal como cloruro de tionilo, en un disolvente inerte, para producir un compuesto de fórmula (VII) en donde L es cloro.

v.) Hacer reaccionar un compuesto de fórmula (X) con un compuesto de fórmula (III), en la cual B, R_{14}, R_{15}, R^c y R^d se definen de acuerdo con una cualquiera de las reivindicaciones 1-5, X es un enlace simple y R_5 es hidrógeno, mientras el compuesto de fórmula (III) tiene protegido su nitrógeno del anillo por t-butiloxicarbonilo, en un disolvente orgánico inerte, en la presencia de un reactivo de acoplamiento y, opcionalmente, una

base orgánica tal como trietilamina o DIPEA, para producir un compuesto de la fórmula general (VIII) después de la desprotección estándar del t-butiloxicarbonilo.

vi) El producto del paso v.) se hace reaccionar con el producto del paso iv.) en un disolvente inerte, opcionalmente en la presencia de una base orgánica tal como trietilamina, para producir un compuesto de fórmula (I), en la cual R_2, R_3, R_4, B, R_{14}, R_{15}, R^c y R^d se definen de acuerdo con una cualquiera de las reivindicaciones 1-4, R_1 es $R_6OC(O)$ y R_6 se define de acuerdo con una cualquiera de las reivindicaciones 1-5, X es un enlace simple, Z está ausente y R_5 es hidrógeno.

35. El proceso de acuerdo con la reivindicación 34 en donde el paso iv.) comprende agregar dimetilformamida a la mezcla de reacción.

36. El proceso de acuerdo con la reivindicación 35 en donde el disolvente inerte en el paso iv.) es tolueno.

37. El proceso de acuerdo con cualquiera de las reivindicaciones 34-36 en donde el disolvente inerte en el paso v.) es THF.

38. El proceso de acuerdo con cualquiera de las reivindicaciones 34-37 en donde el reactivo de acoplamiento en el paso v.) es TBTU.

39. El proceso de acuerdo con cualquiera de las reivindicaciones 34-38 en donde LiCl se agrega a la mezcla de reacción en el paso v.).

40. El proceso de acuerdo con cualquiera de las reivindicaciones 34-39 en donde el paso v.) comprende que el producto se aisle agregando amoníaco disuelto en agua.

41. El proceso de acuerdo con cualquiera de las reivindicaciones 34-40 en donde el producto del paso vi) se purifica y se aisla por recristalización de acetato de etilo.

42. Una composición farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 en combinación con coadyuvantes, diluyentes y/o sustancias portadoras farmacéuticamente aceptables.

43. A compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 para uso en terapia.

44. Uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 para la fabricación de un medicamento para el tratamiento del trastorno de agregación plaquetaria.

45. Uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 para la fabricación de un medicamento para la inhibición del receptor $P2Y_{12}$.

46. Un método de tratamiento de un trastorno de agregación plaquetaria que comprende administrar a un paciente, que sufre de tal desorden, una cantidad terapéuticamente efectiva de un compuesto de acuerdo con cualquiera de las reivindicaciones 1-33.

PCT REQUEST

Original (for SUBMISSION)

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 3.51.005.180 MT/FOP 20060401/0.20.4rc.2.7
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)**	Swedish Patent Office (RO/SE)
0-7	**Applicant's or agent's file reference**	101798-1 WO
I	**Title of Invention**	NEW PYRIDINE ANALOGUES
II	**Applicant**	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	ASTRAZENECA AB
II-5	Address	151 85 Södertälje Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+46 8 553 260 00
II-9	Facsimile No.	+46 8 553 288 20
III-1	**Applicant and/or inventor**	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
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III-1-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-1-6	State of nationality	DK
III-1-7	State of residence	SE

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)	BACH, Peter
III-2-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-2-6	State of nationality	DK
III-2-7	State of residence	SE
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)	BRICKMANN, Kay
III-3-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-3-6	State of nationality	DE
III-3-7	State of residence	SE
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)	GIORDANETTO, Fabrizio
III-4-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-4-6	State of nationality	IT
III-4-7	State of residence	SE
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)	ZETTERBERG, Fredrik
III-5-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-5-6	State of nationality	SE
III-5-7	State of residence	SE

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)	ÖSTERLUND, Krister
III-6-5	Address	AstraZeneca R&D Mölndal 431 83 Mölndal Sweden
III-6-6	State of nationality	SE
III-6-7	State of residence	SE
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 151 85 Södertälje Sweden
IV-1-3	Telephone No.	+46 8 553 260 00
IV-1-4	Facsimile No.	+46 8 553 288 20
IV-1-5	e-mail	patents@astrazeneca.com
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 July 2005 (13.07.2005)
VI-1-2	Number	0501663-9
VI-1-3	Country	SE
VI-2	**Priority claim of earlier national application**	
VI-2-1	Filing date	24 October 2005 (24.10.2005)
VI-2-2	Number	0502354-4
VI-2-3	Country	SE
VII-1	**International Searching Authority Chosen**	Swedish Patent Office (ISA/SE)

PCT REQUEST

Original (for **SUBMISSION**)

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)	5	✓
IX-2	Description	265	-
IX-3	Claims	34	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	305	
	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-11	Copy of general power of attorney	reference no. GF 1572/06	-
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**	Birgitta Larsson	
X-1-1	Name	ASTRAZENECA	
X-1-2	Name of signatory	Birgitta Larsson	
X-1-3	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/SE
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: 105.952

59

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Pais: Suecia

El presente documento oficial

2. ha sido firmado por Anne-Marie Bonde

3. en su calidad de Notario Público

4. y lleva el timbre/sello de Notario Público

en Estocolmo

Lo cual se certifica

5. en Estocolmo **6. el** 17.12.2007

7. por Björn Sandin

Notario Público

8. No 4827

9. Timbre/Sello: **10. Firma:**

NOTARIUS PUBLICUS I STOCKHOLM

BJÖRN SANDIN

999

ASSIGNMENT

The undersigned,

Sören ANDERSEN, Peter BACH, Kay BRICKMANN, Fabrizio GIORDANETTO, Fredrik ZETTERBERG and Krister ÖSTERLUND

domiciled in
AstraZeneca R&D Mölndal S-431 83 Mölndal, Sweden

hereby state under oath to be the sole and true inventor of

NEW PYRIDINE ANALOGUES

We state as well that we 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.

Sören ANDERSEN

Kay BRICKMANN

Fredrik ZETTERBERG

TRASPASO

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 leyes 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.

Peter BACH

Fabrizio GIORDANETTO

Krister ÖSTERLUND

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 17 días del mes de Diciembre 2007, compareci personalmente ante mi, Notario Publico,
Sören Andersen,
Kay Brickmann,
Fredrik Zetterberg,
Peter Bach,
Fabrizio Giordanetto y
Krister Österlund

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)
Anne-Marie Bonde

Ex oficio.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 2007 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 2007, compareci personalmente ante mi, Notario Publico,

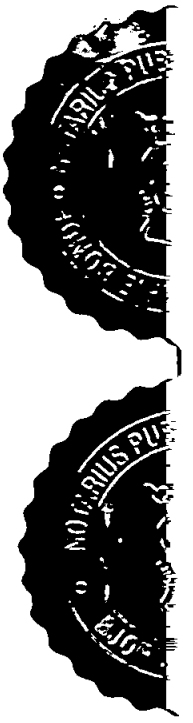
a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 2007 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE





TRADUCCIÓN DE LOS SELLOS QUE SE ENCUENTRAN EN LA APOSTILLA Y EN EL DOCUMENTO DE CESIÓN DE DERECHOS SOBRE LA INVENCIÓN, OTORGADO POR LOS INVENTORES: SÖREN ANDERSEN, PETER BACH, KAY BRICKMANN, FABRIZIO GIORDANETTO, FREDRIK ZETTERBERG Y KRISTER ÖSTERLUND, A LA SOCIEDAD **ASTRAZENECA AB**, DOMICILIADA EN S-151 85 SÖDERTÄLJE, SUECIA, DEL SUECO AL CASTELLANO.

BJÖRN SANDIN
NOTARIO PÚBLICO DE ESTOCOLMO

ANNE- MARIE BONDE
NOTARIO PÚBLICO DE ESTOCOLMO

Brigard & Castro

BOGOTA - COLOMBIA

2
139

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; 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 llevar 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, quotas 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
this 18th day of July 2003

Signature

Name KEVIN BILL

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)

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 (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2007 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)

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)

LEGALIZATION BY APOSTILLE IS REQUIRED.

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**

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.

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



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.

GAVIRIA 229

ORGANIZACIÓN 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	9995

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: Año	2004	Mes	10	Día	30	Hora	04:10 PM	Número de certificado de defunción	A- 2094375.

Presunción de muerte

Juzgado que profirió la sentencia | Fecha de la sentencia: Año | Mes | Día

Documento presentado

Autorización judicial [ ] Certificado Médico [X]

Nombre y cargo del funcionario

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	

Primer testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)	Firma

Segundo testigo

Apellidos y nombres completos

Documentos de Identificación (Clase y número)	Firma

Fecha de inscripción

Año 2004 Mes 11 Día 02

Nombre y firma del funcionario que autoriza

BLANCA LUCIA VALLEJO RESTREPO
NOTARIA 32

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ESPACIO PARA NOTAS

ORIGINAL PARA LA OFICINA DE REGISTRO

OTARIA 32

IRCULO 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 5562241 que expido en la ciudad de Bogotá D.C., hoy 17 NOV 2004

NOTARIA 32 DEL CIRCULO
DE BOGOTA D.C.
NELSON FLOREZ G.
SECRETARIO DELEGADO

NELSON FLOREZ G.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1334 DE 1996

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-012251- -00000-0000

Fecha: 2008-02-07 16:43:01 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 672

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Nova Cortes

rma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

674

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 674

2020
Bogotá D.C.,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	8 12251
	Solicitud internacional	PCT/SE2006/000832
	Fecha inicio fase nacional	13/02/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5593
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 31 MAR. 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11