CSA850663

08 - 1120

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Organo
Oficina de Información y Comercio
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SIC

DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21 **EXPEDIENTE No.** 08-1120

54 **TITULO** DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES

51 **CLASIFICACION INTERNACIONAL** A61K31/44 //A61P3/04 A61P3/06

71 **SOLICITANTE** ASTRAZENECA AB

DOMICILIO SODERTALJE SUECIA

74 **APODERADO** JUAN PABLO CADENA SARMIENTO

22 **SANTAFE DE BOGOTA, D.C.** 08/01/2008

(FORMA P 10)

Oficina de Comunicaciones

PETITORIO

AS: 105.900

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001120- -00000-0000
Fecha: 2008-01-08 16:10:11 Dep. 2020 NUEVA CREACIÓN
Tra. 11 PATENTES Y II Eve. 378 FASE NACIONAL
Act. 411 PRESENTACION Folios: 590

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 Södertälje, 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**: Darren MCKERRECHER, Kurt Gordon PIKE, Michael James WARING. **Dirección:** AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG, GB; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG, GB; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG, GB (Respectivamente). **Nacionalidad o Domicilio**: Gran Bretaña (Respectivamente).	

5 PCT (86)

Solicitud Internacional No. PCT/GB2006/002471 Fecha 03-07-2006
Publicación Internacional No. WO 2007/007041 A1 Fecha 18-01-2007

6 Título (54): DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES

7 Clasificación Internacional (51): A61K31/44 // A61P3/04 // A61P3/06

8 Prioridad

SI ☒ NO ☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
GB	09-07-2005	0514173.4
GB	09-08-2005	0516297.9
GB	24-11-2005	0523862.1
GB	02-12-2005	0524589.9
GB	22-04-2006	0607977.6

9 Comprobante de pago No. 07-104,569;08-706 **Fecha** 08-01-2007

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

2

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 TP 57492 del C.S.J.

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

AS. 105900

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 104,569
FECHA : DICIEMBRE 26 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001120- -00000-0000
Fecha: 2008-01-08 16:10:11 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 590

***** 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.

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 706
FECHA : ENERO 3 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-001120- -00000-0000
Fecha: 2008-01-08 16:10:11 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 590

***** 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	RECIBO DE CAJA			605	03/01/2008	26,145,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998 VALOR COMPLEMENTO TARIFA A#O ANTR	19,000.00
		TOTAL : $	19,000.00

SON: DIEZ Y NUEVE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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): Darren MCKERRECHER, Kurt Gordon PIKE, Michael James WARING.

(74) Agente: JUAN PABLO CADENA SARMIENTO

(30) Prioridad	(31) No. Prioridad	(32 Fecha	(33) País
	0514173.4	09-07-2005	GB
	0516297.9	09-08-2005	GB
	0523862.1	24-11-2005	GB
	0524589.9	02-12-2005	GB
	0607977.6	22-04-2006	GB

(85) Fecha inicio fase nacional: 09-02-2008
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 03-07-2006
No. de solicitud PCT/GB2006/002471

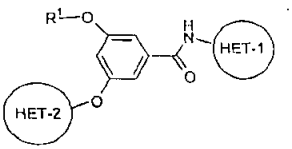
(87) Publicación internacional:
Fecha: 18-01-2007
No. Publicación: WO 2007/007041 A1

FIGURA CARACTERÍSTICA
6 x 6 cm

(54) Titulo: DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES

(55) Reivindicación(es):

1. Un compuesto de formula (I):



(I)

CONTINUA AL RESPALDO ...

en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo; 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2- hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1- fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo enlazado a C, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y, de manera opcional, 1 ó 2 heteroátomos de anillo adicionales, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^7 y/o en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^6;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, qué contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^{10};

...y sus sales y profármacos, son activadores de glucocinasa (GLK) y, en consecuencia, son útiles en el tratamiento, por ejemplo, de diabetes tipo 2. En igual forma, se describen procesos para preparar compuestos de fórmula (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
	0514173.4	09-07-2005	GB
	0516297.9	09-08-2005	GB
	0523862.1	24-11-2005	GB
	0524589.9	02-12-2005	GB
	0607977.6	22-04-2006	GB

(51) Int Cl:

(71) Solicitante (s): **ASTRAZENECA AB**

(72) Inventor(es): Darren MCKERRECHER, Kurt Gordon PIKE, Michael James WARING.

(74) Agente: JUAN PABLO CADENA SARMIENTO

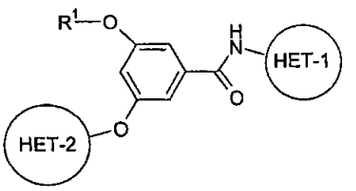
(85) (85) Fecha inicio fase nacional: 09-02-2008
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 03-07-2006
No. de solicitud PCT/GB2006/002471

(87) Publicación internacional
Fecha: 18-01-2007
N° publicación: WO 2007/007041 A1

(54) Titulo: DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES

(55) Reivindicación(es):

1. Un compuesto de formula (I):



(I)

en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1- fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo enlazado a C, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y, de manera opcional, 1 ó 2 heteroátomos de anillo adicionales, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^7 y/o en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^6;

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...y sus sales y profármacos, son activadores de glucocinasa (GLK) y, en consecuencia, son útiles en el tratamiento, por ejemplo, de diabetes tipo 2. En igual forma, se describen procesos para preparar compuestos de fórmula (I).

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE [X] PCT/GB2006/002471 **MODELO DE UTILIDAD** [ ] **DISEÑO INDUSTRIAL** [ ]

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

DOMICILIO SÖDERTÄLJE. SUECIA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) DARREN MCKERRECHER, KURT GORDON PIKE, MICHAEL JAMES WARING.

OTROS

OFICINA DE COMUNICACIONES

105900

4

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

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(51) International Patent Classification:
C07D 417/14 (2006.01) *C07D 405/14* (2006.01)
C07D 401/14 (2006.01) *A61K 31/44* (2006.01)
C07D 403/14 (2006.01) *A61P 3/04* (2006.01)
C07D 413/14 (2006.01) *A61P 3/06* (2006.01)

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(26) Publication Language: English

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0516297.9	9 August 2005 (09.08.2005)	GB
0523862.1	24 November 2005 (24.11.2005)	GB
0524589.9	2 December 2005 (02.12.2005)	GB
0607977.6	22 April 2006 (22.04.2006)	GB

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MC, MD, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NG, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC only)*: **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Södertälje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MCKERRECHER, Darren** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **PIKE, Kurt, Gordon** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **WARING, Michael, James** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; Astrazeneca Ab, S-SE-151 85 Södertälje (SE).

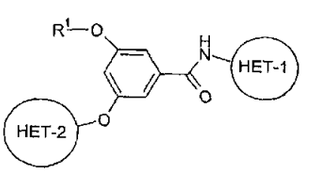
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, 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: HETEROARYL BENZAMIDE DERIVATIVES FOR USE AS GLK ACTIVATORS IN THE TREATMENT OF DIABETES



(I)

(57) Abstract: Compounds of formula (I) wherein R^1, HET-1 and HET-2 are as described in the specification, and their salts and pro-drugs, are activators of glucokinase (GLK) and are thereby useful in the treatment of, for example, type 2 diabetes. Processes for preparing compounds of formula (I) are also described.

WO 2007/007041 A1

HETEROARYL BENZAMIDE DERIVATIVES FOR USE AS GLK ACTIVATORS IN THE TREATMENT OF DIABETES

The present invention relates to a group of benzoyl amino heterocyclyl compounds which are useful in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK or GK), leading to a decreased glucose threshold for insulin secretion. In addition the compounds are predicted to lower blood glucose by increasing hepatic glucose uptake. Such compounds may have utility in the treatment of Type 2 diabetes and obesity. The invention also relates to pharmaceutical compositions comprising said compounds and to methods of treatment of diseases mediated by GLK using said compounds.

In the pancreatic β-cell and liver parenchymal cells the main plasma membrane glucose transporter is GLUT2. Under physiological glucose concentrations the rate at which GLUT2 transports glucose across the membrane is not rate limiting to the overall rate of glucose uptake in these cells. The rate of glucose uptake is limited by the rate of phosphorylation of glucose to glucose-6-phosphate (G-6-P) which is catalysed by glucokinase (GLK) [1]. GLK has a high (6-10mM) Km for glucose and is not inhibited by physiological concentrations of G-6-P [1]. GLK expression is limited to a few tissues and cell types, most notably pancreatic β-cells and liver cells (hepatocytes) [1]. In these cells GLK activity is rate limiting for glucose utilisation and therefore regulates the extent of glucose induced insulin secretion and hepatic glycogen synthesis. These processes are critical in the maintenance of whole body glucose homeostasis and both are dysfunctional in diabetes [2].

In one sub-type of diabetes, Maturity-Onset Diabetes of the Young Type 2 (MODY-2), the diabetes is caused by GLK loss of function mutations [3, 4]. Hyperglycaemia in MODY-2 patients results from defective glucose utilisation in both the pancreas and liver [5]. Defective glucose utilisation in the pancreas of MODY-2 patients results in a raised threshold for glucose stimulated insulin secretion. Conversely, rare activating mutations of GLK reduce this threshold resulting in familial hyperinsulinism [6, 6a, 7]. In addition to the reduced GLK activity observed in MODY-2 diabetics, hepatic glucokinase activity is also decreased in type 2 diabetics [8]. Importantly, global or liver selective overexpression of GLK prevents or reverses the development of the diabetic phenotype in both dietary and genetic models of the disease [9-12]. Moreover, acute

treatment of type 2 diabetics with fructose improves glucose tolerance through stimulation of hepatic glucose utilisation [13]. This effect is believed to be mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

Hepatic GLK activity is inhibited through association with GLK regulatory protein (GLKRP). The GLK/GLKRP complex is stabilised by fructose-6-phosphate (F6P) binding to the GLKRP and destabilised by displacement of this sugar phosphate by fructose-1-phosphate (F1P). F1P is generated by fructokinase mediated phosphorylation of dietary fructose. Consequently, GLK/GLKRP complex integrity and hepatic GLK activity is regulated in a nutritionally dependent manner as F6P is dominant in the post-absorptive state whereas F1P predominates in the post-prandial state. In contrast to the hepatocyte, the pancreatic β-cell expresses GLK in the absence of GLKRP. Therefore, β-cell GLK activity is regulated extensively by the availability of its substrate, glucose. Small molecules may activate GLK either directly or through destabilising the GLK/GLKRP complex. The former class of compounds are predicted to stimulate glucose utilisation in both the liver and the pancreas whereas the latter are predicted to act selectively in the liver. However, compounds with either profile are predicted to be of therapeutic benefit in treating Type 2 diabetes as this disease is characterised by defective glucose utilisation in both tissues.

GLK, GLKRP and the K_{ATP} channel are expressed in neurones of the hypothalamus, a region of the brain that is important in the regulation of energy balance and the control of food intake [14-18]. These neurones have been shown to express orectic and anorectic neuropeptides [15, 19, 20] and have been assumed to be the glucose-sensing neurones within the hypothalamus that are either inhibited or excited by changes in ambient glucose concentrations [17, 19, 21, 22]. The ability of these neurones to sense changes in glucose levels is defective in a variety of genetic and experimentally induced models of obesity [23-28]. Intracerebroventricular (icv) infusion of glucose analogues, that are competitive inhibitors of glucokinase, stimulate food intake in lean rats [29, 30]. In contrast, icv infusion of glucose suppresses feeding [31]. Thus, small molecule activators of GLK may decrease food intake and weight gain through central effects on GLK. Therefore, GLK activators may be of therapeutic use in treating eating disorders, including obesity, in addition to diabetes. The hypothalamic effects will be additive or

synergistic to the effects of the same compounds acting in the liver and/or pancreas in normalising glucose homeostasis, for the treatment of Type 2 diabetes. Thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity).

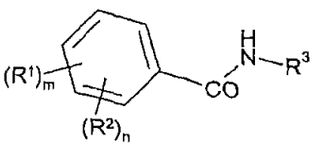
GLK is also expressed in specific entero-endocrine cells where it is believed to control the glucose sensitive secretion of the incretin peptides GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (Glucagon-Like Peptide-1) from gut K-cells and L-cells respectively (32, 33, 34). Therefore, small molecule activators of GLK may have additional beneficial effects on insulin secretion, b-cell function and survival and body weight as a consequence of stimulating GIP and GLP-1 secretion from these entero-endocrine cells.

In WO00/58293 and WO01/44216 (Roche), a series of benzylcarbamoyl compounds are described as glucokinase activators. The mechanism by which such compounds activate GLK is assessed by measuring the direct effect of such compounds in an assay in which GLK activity is linked to NADH production, which in turn is measured optically - see details of the *in vitro* assay described hereinafter. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK.

Further GLK activators have been described in WO03/095438 (substituted phenylacetamides, Roche), WO03/055482 (carboxamide and sulphonamide derivatives, Novo Nordisk), WO2004/002481 (arylcarbonyl derivatives, Novo Nordisk), and in WO03/080585 (amino-substituted benzoylaminoheterocycles, Banyu).

Our International application Number: WO03/000267 describes a group of benzoyl amino pyridyl carboxylic acids which are activators of the enzyme glucokinase (GLK).

Our International application Number: WO03/015774 describes compounds of the Formula (A):



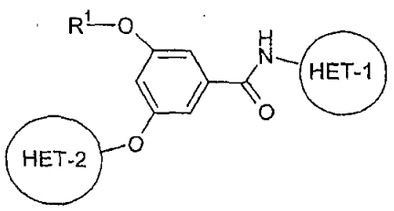
(A)

wherein R^3 is a substituted heterocycle other than a carboxylic acid substituted pyridyl.

International application WO2004/076420 (Banyu) describes compounds which are generally a subset of those described in WO03/015774, wherein for example R^1 is an (substituted) alkyl ether and R^2 is (substituted) phenoxy.

We have surprisingly found a small group of compounds, generally a selected subgroup of those described in WO 03/015774, which have generally superior potency for the GLK enzyme, and more advantageous physical properties, including, for example, higher aqueous solubility, higher permeability, and/or lower plasma protein binding. Consequently, such compounds having a balance of these properties would be expected to display higher plasma free drug levels and superior in vivo efficacy after oral dosing as determined, for example, by activity in Oral Glucose Tolerance Tests (OGTTs). Therefore this group of compounds would be expected to provide superior oral exposure at a lower dose and thereby be particularly suitable for use in the treatment or prevention of a disease or medical condition mediated through GLK. The compounds of the invention may also have superior potency and/or advantageous physical properties (as described above) and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other GLK activators known in the art, as well as those described in WO 03/015774.

Thus, according to the first aspect of the invention there is provided a compound of Formula (I):



(I)

wherein:

R^1 is selected from isopropyl, but-2-yl, cyclopentyl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-hydroxybut-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-methoxybut-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl, 1,1-difluoromethoxyprop-2-yl and 1-trifluoromethoxyprop-2-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^7 and/or on 1 or 2 available carbon atoms by a substituent independently selected from R^6;

HET-2 is a 5- or 6- membered heteroaryl ring, containing 1, 2 or 3 ring hetereoatoms independently selected from O, S and N; which ring is substituted on an available carbon atom by a substituent selected from R^2, and is optionally further substituted on 1 or 2 available carbon atoms by a substituent independently selected from R^3 and/or on an available nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^{10};

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is selected from methyl, trifluoromethyl and halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9; or R^4 and R^5 together with the nitrogen atom to which they are attached form a 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-; which ring is optionally substituted on an available carbon by 1 substituent selected from hydroxy and R^3 or on an available nitrogen atom by methyl;

R^6 is independently selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^7 is independently selected from (1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl, trihalo(1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-

4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl;

R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkylamino, di(1-4C)alkylamino, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, aminocarbonyl, (1-4C)alkylaminocarbonyl, di(1-4C)alkylaminocarbonyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkyl and –S(O)p(1-4C)alkyl;

R^{10} is selected from (1-4C)alkyl, (3-6C)cycloalkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, -C(O)(1-4C)alkyl, benzyl, and (1-4C)alkylsulfonyl;

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

or a salt thereof.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined wherein R^1 is selected from isopropyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-hydroxybut-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-methoxybut-2-yl, 1-fluoromethoxyprop-2-yl, 1,1-difluoromethoxyprop-2-yl and 1-trifluoromethoxyprop-2-yl;

or a salt thereof.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined wherein R^1 is selected from isopropyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-hydroxybut-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-methoxybut-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl, 1,1-difluoromethoxyprop-2-yl and 1-trifluoromethoxyprop-2-yl; or a salt thereof.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined wherein R^3 is halo; or a salt thereof.

In another aspect of the invention there is provided a compound of formula (I) as hereinbefore defined wherein R^7 is independently selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl; or a salt thereof.

It will be appreciated that, where definitions of heterocylyl groups HET-1 and HET-2 encompass heteroaryl rings which may be substituted on nitrogen, such substitution may not result in charged quaternary nitrogen atoms, removal of aromaticity of the ring or unstable structures. It will be appreciated that the definitions of HET-1 and HET-2 are not intended to include any O-O, O-S or S-S bonds. It will be appreciated that the definitions of HET-1 and HET-2 are not intended to include unstable structures.

It will be understood that any single carbon atom in HET-1 may only be substituted by one group R^6 in order to maintain aromaticity of the ring. Up to two different carbon atoms in a HET-1 ring may be substituted by an R^6 group, each of which may be the same or different, provided the structure thereby formed is stable and aromatic.

It will be understood that any single carbon atom in HET-2 may only be substituted by one group R^3 in order to maintain aromaticity of the ring. Up to two different carbon atoms in a HET-2 ring may be substituted by an R^3 group, each of which may be the same or different, provided the structure thereby formed is stable and aromatic.

It will be understood that R^8 can be present on any or all available carbon atoms in the heterocyclic ring formed by NR^4R^5; each carbon atom can be substituted with 1 or 2 R^8 groups which may be the same or different, provided the structure thereby formed is stable (so, for example, it is not intended to cover gem-dihydroxy substitution).

It will be understood that where a compound of the formula (I) contains more than one group R^5, they may be the same or different.

It will be understood that where a compound of the formula (I) contains more than one group R^3, they may be the same or different.

A similar convention applies for all other groups and substituents on a compound of formula (I) as hereinbefore defined.

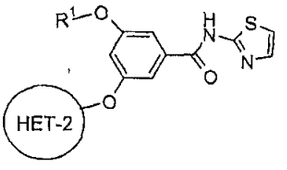
Compounds of Formula (I) may form salts which are within the ambit of the invention. Pharmaceutically acceptable salts are preferred although other salts may be useful in, for example, isolating or purifying compounds.

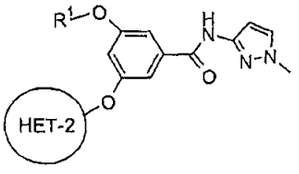
In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pharmaceutically acceptable salt.

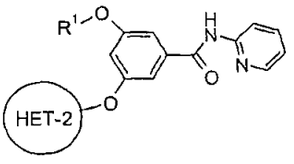
In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual

branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. An analogous convention applies to other generic terms.

For the avoidance of doubt, reference to the group HET-1 containing a nitrogen in the 2-position, is intended to refer to the 2-position relative to the amide nitrogen atom to which the group is attached. For example, HET-1 encompasses but is not limited to the following structures:







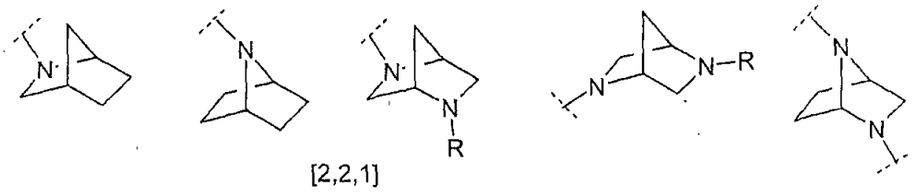
Suitable examples of HET-1 as a 5- or 6-membered, C-linked heteroaryl ring as hereinbefore defined, include thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl.

Suitable examples of HET-2 include thienyl, furyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl and triazolyl. Further suitable examples of HET-2 include aromatic heterocycles where a ring nitrogen or sulfur atom has been oxidised but aromaticity has been preserved, for example a pyridine N-oxide. Further suitable examples of HET-2 include thiazolyl, pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl.

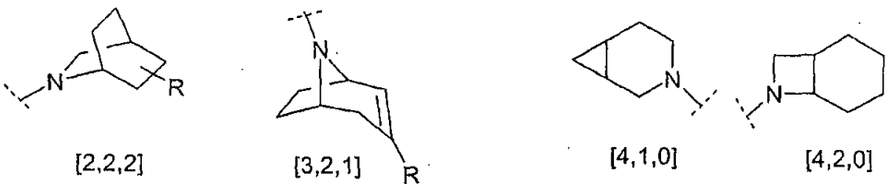
Suitable examples for a 4-7 membered ring formed by R^4 and R^5 together with the nitrogen to which they are attached, as hereinbefore defined, include morpholino, piperidinyl, piperazinyl, pyrrolidinyl, azetidinyl, homopiperazinyl, homo-morpholino, homo-thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group) and homo-piperidinyl. A further suitable example is thiomorpholino (and versions thereof wherein the sulfur is oxidised to an SO or $S(O)_2$ group).

Suitable examples for a 6-10 membered bicyclic heterocyclic ring formed by R^4 and R^5 together with the nitrogen to which they are attached, as hereinbefore defined, are bicyclic saturated or partially unsaturated heterocyclyl ring such as those illustrated by the structures shown below (wherein the dotted line indicates the point of attachment to the

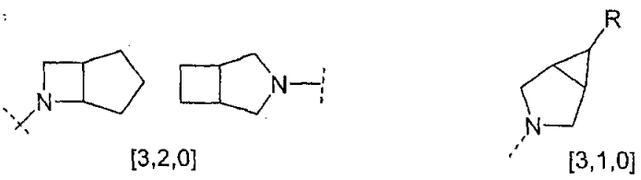
rest of the molecule and wherein R represents the optional substituents for carbon or nitrogen defined hereinbefore):



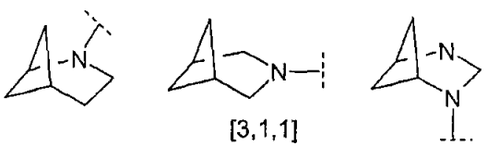
[2,2,1]



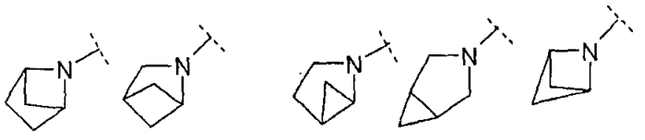
[2,2,2] [3,2,1] [4,1,0] [4,2,0]



[3,2,0] [3,1,0]

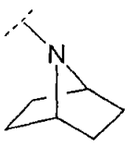


[3,1,1]



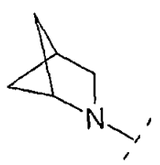
[2,1,1] [3,1,0] [1,1,1]

In particular such a ring system is a [2,2,1] system such as



(7-azabicyclo[2.2.1]hept-7-yl).

In another embodiment, such a ring system is a [2.1.1] system such as



(2-azabicyclo[2.1.1]hex-2-yl).

Examples of **(1-4C)alkyl** include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl; examples of **(3-6C)cycloalkyl** include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl; examples of **halo** include fluoro, chloro, bromo and iodo; examples of **halo(1-4C)alkyl** include fluoromethyl, chloromethyl, fluoroethyl, chloroethyl, fluoropropyl and fluorobutyl; examples of **dihalo(1-4C)alkyl** include difluoromethyl, 1,1-difluoroeth-2-yl, 1,2-difluoroeth-2-yl, 1,1-dichloroeth-2-yl, 1,2-dichloroeth-2-yl, and 1,1-difluoroprop-3-yl; examples of **trihalo(1-4C)alkyl** include trifluoromethyl and 1,1,1-trifluoroeth-2-yl; examples of **hydroxy(1-4C)alkyl** include hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl and 4-hydroxybutyl; examples of **(1-4C)alkoxy(1-4C)alkyl** include methoxymethyl, ethoxymethyl, tert-butoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, methoxypropyl, 2-methoxypropyl and methoxybutyl; example of **(1-4C)alkoxy** include methoxy, ehtoxy, propoxy, isopropxy, butoxy and tert-butoxy; examples of **(1-4C)alkylS(O)p(1-4C)alkyl (where p is 0, 1 or 2)** include methylsulfinylmethyl, ethylsulfinylmethyl, ethylsulfinylethyl, methylsulfinylpropyl, methylsulfinylbutyl, methylsulfonylmethyl, ethylsulfonylmethyl, ethylsulfonylethyl, methylsulfonylpropyl, methylsulfonylbutyl, methylthiomethyl, ethylthiomethyl, ethylthioethyl, methylthiopropyl, and methylthiobutyl; examples of **(1-4C)alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl and tert-butylsulfonyl; examples of **–S(O)p(1-4C)alkyl** include (1-4C)alkylsulfonyl, methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, tert-butylsulfinyl, methylthio, ethylthio, propylthio, isopropylthio and tert-butylthio; examples of **amino(1-4C)alkyl** include aminomethyl, aminoethyl, 2-aminopropyl, 3-aminopropyl, 1-aminoisopropyl and 4-aminobutyl; examples of **(1-4C)alkylamino(1-4C)alkyl** include (N-methyl)aminomethyl, (N-ethyl)aminomethyl, 1-((N-methyl)amino)ethyl, 2-((N-methyl)amino)ethyl, (N-ethyl)aminoethyl, (N-methyl)aminopropyl, and 4-((N-methyl)amino)butyl; examples of **di(1-4C)alkylamino(1-4C)alkyl** include

dimethylaminomethyl, methyl(ethyl)aminomethyl, methyl(ethyl)aminoethyl, (N,N-diethyl)aminoethyl, (N,N-dimethyl)aminopropyl and (N,N-dimethyl)aminobutyl; examples of **–C(O)(1-4C)alkyl** and **(1-4C)alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl and tert-butyl carbonyl; examples of **(1-4C)alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, butylamino and tert-butylamino; examples of **di(1-4C)alkylamino** include dimethylamino, diethylamino, N-methyl-N-ethylamino, dipropylamino, N-isopropyl-N-methyamino and dibutylamino; examples of **(1-4C)alkylaminocarbonyl** include methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl, isopropylaminocarbonyl, butylaminocarbonyl and tert-butylaminocarbonyl; examples of **di(1-4C)alkylaminocarbonyl** include dimethylaminocarbonyl, diethylaminocarbonyl, N-methyl-N-ethylaminocarbonyl, dipropylaminocarbonyl, N-isopropyl-N-methyaminocarbonyl and dibutylaminocarbonyl.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of stimulating GLK directly or inhibiting the GLK/GLKRP interaction. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. It is also to be understood that certain compounds may exist in tautomeric forms and that the invention also relates to any and all tautomeric forms of the compounds of the invention which activate GLK.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which activate GLK.

In another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (I) are in-vivo hydrolysable esters of compounds of formula (I). Therefore in another aspect, the invention relates to compounds of formula (I) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

In one embodiment of the invention are provided compounds of formula (I), in an

alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (I), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (I), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (I).

The compounds of the invention may be administered in the form of a pro-drug. A pro-drug is a bioprecursor or pharmaceutically acceptable compound being degradable in the body to produce a compound of the invention (such as an ester or amide of a compound of the invention, particularly an in-vivo hydrolysable ester). Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

The contents of the above cited documents are incorporated herein by reference.

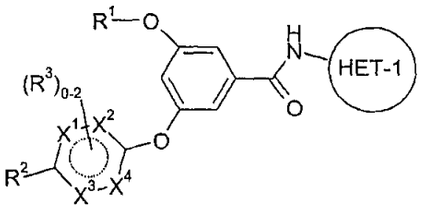
Examples of pro-drugs are as follows. An in-vivo hydrolysable ester of a compound of the invention containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C_1 to C_6alkoxymethyl esters for example methoxymethyl, C_1 to C_6alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_3 to C_8cycloalkoxycarbonyloxyC_1 to C_6alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the invention containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as

a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a benzoxazinone derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

In a further aspect of the invention there is provided a compound of formula (I) which is a compound of formula (IA), or a salt thereof:



(IA)

wherein each of X^1, X^2 and X^3 is independently selected from CH, N, S and O;

X^4 is absent (to make a 5-membered ring) or is selected from CH, N, O and S;

provided that at least one of X^1, X^2, X^3 and X^4 is CH and provided that there are no O-O, O-S or S-S bonds within the ring;

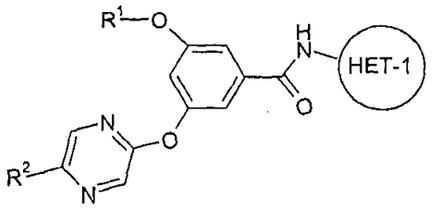
R^3, if present, is selected from methyl, trifluoromethyl and halo;

R^1, R^2 and HET-1 are as defined for a compound of formula (I).

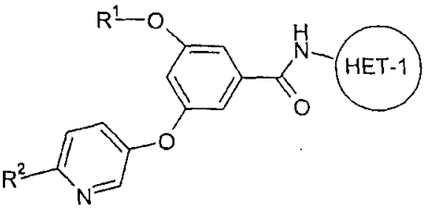
It will be understood that the dotted circle inside the ring containing X^1 to X^4 (that is, the HET-2 ring) is intended to indicate that the ring is aromatic, although the precise number and position of the double bonds will be dependent on the nature of X^1 to X^4.

References herein to a compound of formula (I) should generally be understood to apply equally to a compound of formula (IA), whether explicitly stated or not, unless the context indicates otherwise.

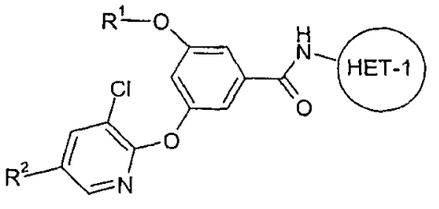
Particular examples of compounds of formula (I) and (IA) include compounds of formulae (IB), (IC) and/or (ID):



(IB)



(IC)



(ID)

wherein R^1, R^2 and HET-1 are as defined for a compound of formula (I).

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) or (IA). Further, each of the following values may be used in combination with one or more of the other following values to limit the broadest defintion of formula (I) or (IA) or to limit any narrower definitions of formula (I) or (IA) in any of the aspects hereinbefore or hereinafter. Where appropriate each of the following values may also be used to limit any definition within formulae (IB), (IC) and/or (ID).

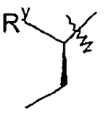
(1) R^1 is of sub-formula X:



(X)

wherein R^x is selected from methyl, ethyl, trifluoromethyl, ethynyl, hydroxymethyl, hydroxyethyl, methoxymethyl, fluoromethoxymethyl, difluoromethoxymethyl and trifluoromethoxymethyl; preferably R^x is selected from methyl, ethyl, trifluoromethyl, ethynyl, hydroxymethyl, hydroxyethyl, methoxymethyl, fluoromethoxymethyl and difluoromethoxymethyl

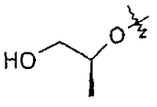
(2) R^1 is of sub-formula Y:



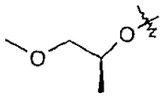
(Y)

wherein R^y is selected from hydroxymethyl and methoxymethyl

(3) R^1 is 1-hydroxyprop-2-yl and the configuration is preferably (S), that is R^1-O- is:



(4) R^1 is 1-methoxyprop-2-yl and the configuration is preferably (S), that is R^1-O- is:

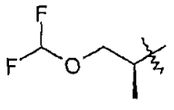


(5) R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, hydroxybut-3-yl and 1-methoxyprop-2-yl

(6) R^1 is 1,1,1-trifluoroprop-2-yl, 1-fluoromethoxyprop-2-yl, 1,1-difluoromethoxyprop-2-yl or 1-trifluoromethoxyprop-2-yl

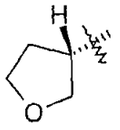
(7) R^1 is 1-fluoromethoxyprop-2-yl, 1,1-difluoromethoxyprop-2-yl or 1-trifluoromethoxyprop-2-yl, particularly 1-fluoromethoxyprop-2-yl or 1,1-difluoromethoxyprop-2-yl

(8) R^1 is 1,1-difluoromethoxyprop-2-yl, particularly with the stereochemistry:

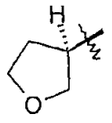


(9) R^1 is tetrahydrofuryl or tetrahydropyranyl

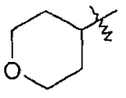
(10) R^1 is tetrahydrofuryl in the (S) configuration, that is:



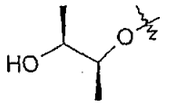
(11) R^1 is tetrahydrofuryl in the (R) configuration, that is:



(12) R^1 is 4-tetrahydropyranyl:



(13) R^1 is 2-hydroxy-but-3-yl and the configuration is preferably such that R^1-O- is:



(14) R^1 is 1-hydroxybut-2-yl or 1-methoxybut-2-yl

(15) R^1 is selected from isopropyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-fluoromethoxyprop-2-yl, 1,1-difluoromethoxyprop-2-yl and 1-trifluoromethoxyprop-2-yl

(16) R^1 is selected from 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl and 2-methoxybut-1-yl

(17) R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1,1-difluoromethoxyprop-2-yl, tetrahydrofuryl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl

(18) R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1,1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl

(19) R^1 is selected from tetrahydrofuryl, 1-difluoromethoxyprop-2-yl, 1,3-difluoroprop-2-yl, and 2-hydroxybut-3-yl

(20) R^1 is selected from isopropyl, tetrahydrofuryl, 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl

(21) R^1 is selected from 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl, for example (2*S*)-1-hydroxyprop-2-yl and (2*S*)-1-methoxyprop-2-yl

(22) R^1 is selected from isopropyl, but-2-yl, cyclopentyl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-hydroxybut-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-methoxybut-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl

(23) R^1 is selected from isopropyl, but-2-yl, cyclopentyl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-hydroxybut-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-methoxybut-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl and 1,1-difluoromethoxyprop-2-yl

(24) HET-1 is a 5-membered heteroaryl ring

(25) HET-1 is a 6-membered heteroaryl ring

(26) HET-1 is substituted with 1 or 2 substituents independently selected from R^6

(27) HET-1 is substituted with 1 substituent selected from R^6

(28) HET-1 is substituted with 1 substituent selected from R^7

(29) HET-1 is unsubstituted

(30) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl, oxadiazolyl, and triazolyl

(31) HET-1 is selected from thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl and oxadiazolyl

(32) HET-1 is selected from pyridyl, pyrazinyl, pyridazinyl and pyrimidinyl

(33) HET-1 is selected from thiazolyl, pyrazolyl and oxazolyl

(34) HET-1 is selected from thiadiazolyl and oxadiazolyl

(35) HET-1 is selected from 1,3,4-thiadiazolyl and 1,3,4-oxadiazolyl

(36) HET-1 is selected from 1,2,4-oxadiazolyl and 1,2,4-oxadiazolyl

(37) HET-1 is pyrazolyl, particularly N-methylpyrazolyl

(38) HET-1 is pyrazinyl

(39) HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl

(40) HET-1 is selected from thiazolyl, pyrazolyl, and thiadiazolyl, optionally substituted with (1-4C)alkyl

(41) HET-1 is pyrazolyl, particularly N-methylpyrazolyl

(42) HET-1 is pyrazolyl (optionally substituted with ethyl, isopropyl or 1 or 2 methyl), thiazolyl (optionally substituted with methyl), pyrazinyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro), isoxazolyl (optionally substituted with methyl) and thiadiazolyl (optionally substituted with methyl)

(43) HET-1 is pyrazolyl (optionally substituted with ethyl, isopropyl, difluoromethyl, or 1 or 2 methyl), thiazolyl (optionally substituted with methyl), pyrazinyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro), isoxazolyl (optionally substituted with methyl) and thiadiazolyl (optionally substituted with methyl)

(44) HET-1 is selected from pyrazinyl (optionally substituted with methyl), pyrazolyl (optionally substituted on carbon by methyl), methylthiadiazolyl (particularly 1,2,4-thiadiazol-5-yl, more particularly 3-methyl-1,2,4-thiadiazol-5-yl), thiazolyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro) and isoxazolyl

(45) HET-1 is N-difluoromethylpyrazolyl

(46) HET-1 is 5-methylpyrazin-2-yl

(47) HET-1 is pyrazolyl (optionally substituted with ethyl, isopropyl, difluoromethyl, or 1 or 2 methyl), thiazolyl (optionally substituted with methyl), pyrazinyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro), isoxazolyl (optionally substituted with methyl) and thiadiazolyl (optionally substituted with methyl); and

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1,1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl; when HET-1 is pyrazolyl unsubstituted on nitrogen (ie NH-pyrazolyl), particularly R^1 is selected from 1-methoxyprop-2-yl, isopropyl, and tetrahydrofuryl

(48) HET-1 is pyrazolyl (optionally substituted on carbon with methyl), thiazolyl (optionally substituted with methyl), pyrazinyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro), isoxazolyl and methylthiadiazolyl (particularly 3-methyl-1,2,4-thiadiazol-5-yl);

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1,1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl; when HET-1 is pyrazolyl, particularly R^1 is selected from 1-methoxyprop-2-yl, isopropyl, and tetrahydrofuryl

(49) HET-1 is methylpyrazinyl and R^1 is selected from 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl, for example (2*S*)-1-hydroxyprop-2-yl and (2*S*)-1-methoxyprop-2-yl

(50) HET-1 is pyrazolyl and R^1 is selected from isopropyl, tetrahydrofuryl and 1-methoxyprop-2-yl, for example (2*S*)-1-methoxyprop-2-yl

(51) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl

(52) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(53) R^6 is selected from (1-4C)alkyl, halo, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(54) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, hydroxymethyl and methoxymethyl

(55) R^6 is selected from methyl, ethyl, chloro and fluoro

(56) R^6 is methyl or fluoro, preferably methyl

(57) R^6 is selected from methyl, ethyl, bromo, chloro, fluoro, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(58) R^6 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(59) R^6 is selected from methyl, ethyl, isopropyl and methoxymethyl

(60) when 2 substituents R^6 are present, both are selected from methyl, ethyl, bromo, chloro and fluoro; preferably both are methyl

(61) R^6 is selected from (1-4C)alkylS(O)p(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl

(62) R^7 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl and di(1-4C)alkylamino(1-4C)alkyl

(63) R^7 is selected from methyl, ethyl, hydroxymethyl, methoxymethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl

(64) R^7 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkylS(O)p(1-4C)alkyl, amino(1-4C)alkyl, (1-4C)alkylamino(1-4C)alkyl, and di(1-4C)alkylamino(1-4C)alkyl

(65) R^7 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, and dimethylaminomethyl

(66) R^7 is selected from methyl, ethyl, hydroxymethyl and methoxymethyl

(67) R^7 is selected from methyl, isopropyl and ethyl

(68) R^7 is selected from methyl, isopropyl, difluoromethyl and ethyl

(69) R^7 is selected from isopropyl and difluoromethyl, particularly difluoromethyl

(70) R^7 is selected from methyl and ethyl

(71) R^7 is methyl

(72) R^7 is selected from methyl, ethyl, aminomethyl, N-methylaminomethyl, dimethylaminomethyl, hydroxymethyl and methoxymethyl

(73) R^7 is selected from methyl, ethyl, isopropyl and methoxymethyl

(74) when R^7 is selected from halo(1-4C)alkyl, dihalo(1-4C)alkyl and trihalo(1-4C)alkyl, each halo is selected from chloro and fluoro, and is in particular fluoro.

(75) when R^7 is selected from halo(1-4C)alkyl, dihalo(1-4C)alkyl and trihalo(1-4C)alkyl, R^7 is particularly selected from fluoromethyl, difluoroethyl, difluoromethyl and trifluoromethyl

(76) HET-2 is a 5-membered ring

(77) HET-2 is a 6-membered ring

(78) HET-2 is selected from thienyl, furyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl, oxazolyl, isoxazolyl and oxadiazolyl

(79) HET-2 is selected from thienyl, furyl, thiadiazolyl, pyridyl, pyrazinyl, pyridazinyl, pyrazolyl, imidazolyl, pyrimidinyl and oxadiazolyl

(80) HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and thienyl

(81) HET-2 is selected from pyridyl, pyrazinyl and thiazolyl

(82) HET-2 is selected from pyridyl, pyrazinyl, pyridazinyl and thiazolyl

(83) HET-2 is selected from pyridyl and pyrazinyl

(84) HET-2 is pyrazinyl

(85) HET-2 is substituted with a substituent selected from R^3

(86) HET-2 has one nitrogen substituent selected from R^{10}

(87) R^3 is chloro or fluoro

(88) R^3 is chloro

(89) R^3 is fluoro

(90) R^3 is chloro or methyl

(91) R^3 is fluoro, chloro or methyl

(92) R^2 is $-C(O)NR^4R^5$

(93) R^2 is $-SO_2NR^4R^5$

(94) R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 membered ring

(95) R^4 and R^5 together with the nitrogen atom to which they are attached form a 5 membered ring

(96) R^4 and R^5 together with the nitrogen atom to which they are attached form a 6 membered ring

(97) R^4 and R^5 together with the nitrogen atom to which they are attached form a 7 membered ring

(98) R^4 and R^5 together with the nitrogen atom to which they are attached form a fully saturated ring

(99) R^4 and R^5 together with the nitrogen atom to which they are attached form a ring selected from morpholino, piperidinyl, piperazinyl, pyrrolidinyl and azetidinyl

(100) R^4 and R^5 together with the nitrogen atom to which they are attached form a ring selected from pyrrolidinyl, morpholino and azetidinyl

(101) R^4 and R^5 together with the nitrogen atom to which they are attached form a ring selected from 7-azabicyclo[2.2.1]hept-7-yl, pyrrolidinyl, morpholino and azetidinyl

(102) R^4 and R^5 together with the nitrogen atom to which they are attached form an azetidinyl ring

(103) R^4 and R^5 together with the nitrogen atom to which they are attached form an azetidinyl or pyrrolidinyl ring

(104) R^4 and R^5 together with the nitrogen atom to which they are attached form an unsubstituted ring

(105) R^4 and R^5 together with the nitrogen atom to which they are attached form an ring mono-substituted either with a substituent R^8 or with a substituent R^9

(106) R^4 and R^5 together with the nitrogen atom to which they are attached form a 6-10 membered bicyclic saturated or partially unsaturated ring

(107) R^8 is selected from hydroxy, (1-4C)alkoxy, (1-4C)alkyl

(108) R^8 is selected from hydroxy, methoxy and methyl

(109) R^9 is selected from (1-4C)alkyl and –C(O)(1-4C)alkyl

(110) R^2 is azetidinylcarbonyl or pyrrolidinylcarbonyl, preferably azetidinylcarbonyl

(109) R^{10} is (1-4C)alkyl

(111) R^{10} is (3-6C)cycloalkyl

(112) R^{10} is hydroxy(1-4C)alkyl or (1-4C)alkoxy(1-4C)alkyl

(113) R^{10} is -C(O)(1-4C)alkyl

(114) R^{10} is benzyl

(115) R^{10} is (1-4C)alkylsulfonyl

(116) R^{10} is (1-4C)alkyl or benzyl

According to a further feature of the invention there is provided the following preferred groups of compounds of the invention:

In one aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a methyl or ethyl group and/or on 1 or 2 available carbon atoms by a methyl or ethyl group;

HET-2 is a 5- or 6- membered heteroaryl ring, containing 1, 2 or 3 ring hetereoatoms independently selected from O, S and N; which ring is substituted on an available carbon

atom by a substituent selected from R^2, and is optionally further substituted on 1 or 2 available carbon atoms by a substituent independently selected from R^3 and/or on an available nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^{10};

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is selected from halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, and $-S(O)p$(1-4C)alkyl;

R^{10} is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, benzyl, and (1-4C)alkylsulfonyl;

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

In one aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a methyl or ethyl group and/or on 1 or 2 available carbon atoms by a methyl or ethyl group;

HET-2 is a 5- or 6- membered heteroaryl ring, containing 1, 2 or 3 ring hetereoatoms independently selected from O, S and N; which ring is substituted on an available carbon atom by a substituent selected from R^2, and is optionally further substituted on 1 or 2 available carbon atoms by a substituent independently selected from R^3 and/or on an

available nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^{10};

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is selected from halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, and $-S(O)_p$(1-4C)alkyl;

R^{10} is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, benzyl, and (1-4C)alkylsulfonyl;

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

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, cyclopentyl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a methyl, ethyl or isopropyl group and/or on 1 or 2 available carbon atoms by a methyl, ethyl or fluoro group;

HET-2 is a 5- or 6- membered heteroaryl ring, containing 1, 2 or 3 ring hetereoatoms independently selected from O, S and N; which ring is substituted on an available carbon atom by a substituent selected from R^2, and is optionally further substituted on 1 or 2 available carbon atoms by a substituent independently selected from R^3 and/or on an

available nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^{10};

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is selected from halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, and –S(O)p(1-4C)alkyl;

R^{10} is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, benzyl, and (1-4C)alkylsulfonyl;

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

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, cyclopentyl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a methyl, ethyl or isopropyl group and/or on 1 or 2 available carbon atoms by a methyl, ethyl or fluoro group;

HET-2 is a 5-or 6- membered heteroaryl ring, containing 1, 2 or 3 ring hetereoatoms independently selected from O, S and N; which ring is substituted on an available carbon atom by a substituent selected from R^2, and is optionally further substituted on 1 or 2 available carbon atoms by a substituent independently selected from R^3 and/or on an

available nitrogen atom (provided it is not thereby quaternised) by a substituent selected from R^{10};

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is selected from methyl and halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; which ring is optionally substituted on an available carbon atom by 1 or 2 substituents independently selected from R^8 and/or on an available nitrogen atom by a substituent selected from R^9;

R^8 is selected from hydroxy, (1-4C)alkoxy and (1-4C)alkyl;

R^9 is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, and $-S(O)_p$(1-4C)alkyl;

R^{10} is selected from (1-4C)alkyl, -C(O)(1-4C)alkyl, benzyl, and (1-4C)alkylsulfonyl;

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

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, cyclopentyl, 1,1,1-trifluoroprop-2-yl, 1,3-difluoroprop-2-yl, but-1-yn-3-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, tetrahydrofuryl, tetrahydropyranyl, 1-methoxyprop-2-yl, 2-hydroxyprop-1-yl, 2-methoxyprop-1-yl, 2-hydroxybut-1-yl, 2-methoxybut-1-yl, 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is a 5- or 6-membered, C-linked heteroaryl ring containing a nitrogen atom in the 2-position and optionally 1 or 2 further ring heteroatoms independently selected from O, N and S; which ring is optionally substituted on any nitrogen atom (provided it is not thereby quaternised) by a methyl, ethyl or isopropyl group and/or on 1 or 2 available carbon atoms by a methyl, ethyl or fluoro group;

HET-2 is a 5- or 6- membered heteroaryl ring, containing 1, 2 or 3 ring hetereoatoms independently selected from O, S and N; which ring is substituted on an available carbon atom by a substituent selected from R^2, and is optionally further substituted on 1 or 2 available carbon atoms by a substituent independently selected from R^3;

R^2 is selected from $-C(O)NR^4R^5$ and $-SO_2NR^4R^5$;

R^3 is selected from methyl and halo;

R^4 and R^5 together with the nitrogen atom to which they are attached form a 4 to 7 membered saturated or partially unsaturated heterocyclyl ring, optionally containing 1 or 2 further heteroatoms (in addition to the linking N atom) independently selected from O, N and S, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and wherein a sulphur atom in the ring may optionally be oxidised to a S(O) or $S(O)_2$ group; or

R^4 and R^5 together with the nitrogen atom to which they are attached form a 6-10 membered bicyclic saturated or partially unsaturated heterocyclyl ring, optionally containing 1 further nitrogen atom (in addition to the linking N atom), wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, 1,3-difluoroprop-2-yl, 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl and tetrahydrofuryl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is a substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is a substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is a substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl or pyrrolidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl,

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and thienyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted with a methyl, isopropyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl, pyridyl, isoxazolyl and pyrazinyl, wherein R^1 is optionally substituted with a methyl, isopropyl or ethyl group and/or (on a carbon atom) by fluoro;

HET-2 is selected from pyridyl, pyrazinyl, pyridazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl or pyrrolidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl, pyridyl, isoxazolyl and pyrazinyl, wherein R^1 is optionally substituted with a methyl, isopropyl or ethyl group and/or (on a carbon atom) by fluoro;

HET-2 is selected from pyridyl, pyrazinyl, pyridazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is methyl, fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, 7-azabicyclo[2.2.1]hept-7-yl, morpholino, or pyrrolidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl, pyridyl, isoxazolyl and pyrazinyl, wherein R^1 is optionally substituted with a methyl, isopropyl or ethyl group and/or (on a carbon atom) by fluoro;

HET-2 is selected from pyridyl, pyrazinyl, pyridazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is methyl, fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl or pyrrolidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl, pyridyl, isoxazolyl and pyrazinyl, wherein R^1 is optionally substituted on a nitrogen atom with methyl, difluoromethyl, isopropyl or ethyl and/or on a carbon atom by fluoro or methyl; provided that when HET-1 is pyrazolyl, R^1 is selected from 1-methoxyprop-2-yl, isopropyl, and tetrahydrofuryl;

HET-2 is selected from pyridyl, pyrazinyl, pyridazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is methyl, fluoro or chloro;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$, particularly $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, 7-azabicyclo[2.2.1]hept-7-yl, morpholino, or pyrrolidinyl ring.

In another aspect, Aspect A, of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from pyrazinyl (optionally substituted with methyl), pyrazolyl (optionally substituted on carbon by methyl), methylthiadiazolyl (particularly 3-methyl-1,2,4-thiadiazol-5-yl), thiazolyl (optionally substituted with methyl), pyridyl (optionally

substituted by fluoro) and isoxazolyl; provided that when HET-1 is pyrazolyl, particularly R^1 is selected from 1-methoxyprop-2-yl, isopropyl, and tetrahydrofuryl;
HET-2 is selected from pyridyl, pyrazinyl, pyridazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;
R^3 is methyl, fluoro or chloro;
R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$, particularly $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl, 7-azabicyclo[2.2.1]hept-7-yl, morpholino, or pyrrolidinyl ring.

In another aspect, Aspect B, of the invention there is provided a compound of formula (I) or (IA) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from isopropyl, cyclopentyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, tetrahydropyranyl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;
HET-1 is selected from pyrazinyl (optionally substituted with methyl), pyrazolyl (optionally substituted on carbon by methyl), methylthiadiazolyl (particularly 3-methyl-1,2,4-thiadiazol-5-yl), thiazolyl (optionally substituted with methyl), pyridyl (optionally substituted by fluoro) and isoxazolyl; provided that when HET-1 is pyrazolyl, particularly R^1 is selected from 1-methoxyprop-2-yl, isopropyl, and tetrahydrofuryl;
HET-2 is selected from pyridyl and pyrazinyl, substituted by R^2 and optionally substituted by R^3;
R^3 is methyl, fluoro or chloro;
R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$, particularly $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl or pyrrolidinyl ring, particularly azetidinyl.
Particular compounds of Aspect B are those of formulae (IB), (IC) and/or (ID).

In another aspect, Aspect C, of the invention there is provided a compound of formula (IB), (IC) or (ID) as hereinbefore defined, or a salt thereof, wherein:
R^1 is selected from isopropyl, 1-hydroxyprop-2-yl, tetrahydrofuryl and 1-methoxyprop-2-yl; (particularly R^1 is selected from isopropyl, (2S)-1-hydroxyprop-2-yl, tetrahydrofuryl and (2S)-1-methoxyprop-2-yl);
HET-1 is methylpyrazinyl;
R^2 is $-CONR^4R^5$;
R^4 and R^5 together form an azetidinyl ring.

In another aspect, Aspect D, of the invention there is provided a compound of formula (IB) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1-hydroxyprop-2-yl, tetrahydrofuryl and 1-methoxyprop-2-yl; (particularly R^1 is selected from isopropyl, (2S)-1-hydroxyprop-2-yl, tetrahydrofuryl and (2S)-1-methoxyprop-2-yl);

HET-1 is methylpyrazinyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl ring.

In another aspect, Aspect E, of the invention there is provided a compound of formula (IB), (IC) or (ID) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, tetrahydrofuryl and 1-methoxyprop-2-yl (particularly (2S)-1-methoxyprop-2-yl);

HET-1 is pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl ring.

In another aspect, Aspect F, of the invention there is provided a compound of formula (IB) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, tetrahydrofuryl and 1-methoxyprop-2-yl (particularly (2S)-1-methoxyprop-2-yl);

HET-1 is pyrazolyl;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, but-2-yl, 1,3-difluoroprop-2-yl, 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl and tetrahydrofuryl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, 1-hydroxyprop-2-yl and 1-methoxyprop-2-yl,

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and thienyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted with a methyl, isopropyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from isopropyl, 1,3-difluoroprop-2-yl, but-2-yl, 1-hydroxyprop-2-yl, 2-hydroxybut-3-yl, 1-difluoromethoxyprop-2-yl, tetrahydrofuryl, 1-hydroxybut-2-yl and 1-methoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted with a methyl, isopropyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and pyrimidinyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$ or $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In one aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and thienyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-CONR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In one aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

HET-2 is an optionally substituted 5- or 6-membered heteroaryl ring as hereinbefore defined;

R^2 is $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

In another aspect of the invention there is provided a compound of formula (I) (or IA) as hereinbefore defined, or a salt thereof, wherein:

R^1 is selected from 1-fluoromethoxyprop-2-yl and 1,1-difluoromethoxyprop-2-yl;

HET-1 is selected from thiazolyl, pyrazolyl, thiadiazolyl and pyrazinyl, wherein R^1 is optionally substituted on carbon or nitrogen with a methyl or ethyl group;

HET-2 is selected from pyridyl, pyrazinyl, thiazolyl and thienyl, substituted by R^2 and optionally substituted by R^3;

R^3 is fluoro or chloro;

R^2 is $-SO_2NR^4R^5$;

R^4 and R^5 together form an azetidinyl, pyrrolidinyl or morpholino ring.

Further preferred compounds of the invention are each of the Examples (and salts thereof), each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples (and salts thereof).

Particular compounds of the invention include any one or more of:

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-1,3-thiazol-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-1,3-thiazol-2-ylbenzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-1,3-thiazol-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]-N-1,3-thiazol-2-ylbenzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1,3-thiazol-2-ylbenzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;
3-{[5-(azetidin-1-ylsulfonyl)pyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[3-chloro-5-(morpholin-4-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and
3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or
3-{[5-(azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[2-(azetidin-1-ylcarbonyl)pyrimidin-5-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[2-(azetidin-1-ylcarbonyl)pyrimidin-5-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H- pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-[1-(1-methylethyl)-1H-pyrazol-3-yl]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[4-(azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[4-(azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-(hydroxymethyl)propyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide; and/or

3-{[2-(azetidin-1-ylcarbonyl)pyrimidin-5-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1,3-thiazol-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-(cyclopentyloxy)-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1R,2R)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S,2S)-2-hydroxy-1-methylpropyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[4-(azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(5-methylpyrazin-2-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1,3-thiazol-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyridin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(1-methylethyl)oxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(1-methylethyl)oxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-[1-(1-methylethyl)-1H-pyrazol-3-yl]-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(1-methylethyl)oxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyridin-2-ylbenzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-isoxazol-3-yl-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]-N-1H-pyrazol-3-ylbenzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1,5-dimethyl-1H-pyrazol-3-yl)-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1,5-dimethyl-1H-pyrazol-3-yl)-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridazin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(4-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-[1-(1-methylethyl)-1H-pyrazol-3-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-1H-pyrazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(1,5-dimethyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(4-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(5-methyl-1,3-thiazol-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(5-methylpyrazin-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-ethyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-[1-(1-methylethyl)-1H-pyrazol-3-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-1H-pyrazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(5-methylpyrazin-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(5-methylpyrazin-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(5-fluoropyridin-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[3-chloro-5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-(5-methylpyrazin-2-yl)benzamide;

3-{[3-chloro-5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[3-chloro-5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(5-methylpyrazin-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(5-methylpyrazin-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(5-methylpyrazin-2-yl)-5-(tetrahydro-2H-pyran-4-yloxy)benzamide; and

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide; and/or

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-isoxazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-pyrazin-2-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(5-fluoropyridin-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyridin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-isoxazol-3-yl-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(4-methyl-1,3-thiazol-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methyl-1,3-thiazol-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyrazin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-pyrazin-2-ylbenzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyrazin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-pyrazin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyrazin-2-ylbenzamide;

3-{[3-chloro-5-(morpholin-4-ylcarbonyl)pyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(7-azabicyclo[2.2.1]hept-7-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide; and

3-{[5-(azetidin-1-ylcarbonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide; and/or

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-pyrazin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-pyridin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

N-(1-methyl-1H-pyrazol-3-yl)-3-{[6-(pyrrolidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-pyrazin-2-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(5-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-1H-pyrazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(5-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-1H-pyrazol-3-ylbenzamide;
3-{[5-(azetidin-1-ylsulfonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-[1-(difluoromethyl)-1H-pyrazol-3-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-[1-(difluoromethyl)-1H-pyrazol-3-yl]-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-[1-(difluoromethyl)-1H-pyrazol-3-yl]-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide; and/or
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*R*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*R*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide;
or a salt thereof.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I), (IA), (IB), (IC) or (ID) as defined above, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically-acceptable diluent or carrier.

According to another aspect of the invention there is provided the a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament.

According to another aspect of the invention there is provided the a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

Further according to the invention there is provided the use a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof in the preparation of a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

The compound is suitably formulated as a pharmaceutical composition for use in this way.

According to another aspect of the present invention there is provided a method of treating GLK mediated diseases, especially diabetes, by administering an effective amount of a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Specific diseases which may be treated by a compound or composition of the invention include: blood glucose lowering in Type 2 Diabetes Mellitus without a serious risk of hypoglycaemia (and potential to treat type 1), dyslipidemia, obesity, insulin resistance, metabolic syndrome X, impaired glucose tolerance.

As discussed above, thus the GLK/GLKRP system can be described as a potential "Diabesity" target (of benefit in both Diabetes and Obesity). Thus, according to another aspect of the invention there is provided the use of a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the combined treatment or prevention, particularly treatment of diabetes and obesity.

According to another aspect of the invention there is provided the use of a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for use in the treatment or prevention, particularly treatment of obesity.

According to another aspect of the invention there is provided the a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof as defined above for use as a medicament for treatment or prevention, particularly treatment of obesity.

According to a further aspect of the invention there is provided a method for the combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

According to a further aspect of the invention there is provided a method for the treatment of obesity by administering an effective amount of a compound of Formula (I), (IA), (IB), (IC) or (ID) or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

Compounds of the invention may be particularly suitable for use as pharmaceuticals because of advantageous physical and/or pharmacokinetic properties, and/or favourable toxicity profile and/or favourable metabolic profile.

Favourable toxicity profile may be demonstrated, for example, by use of an Ames test assay, and/or by testing against the hERG ion channel. A favourable metabolic profile may mean, for example, reduced rate of metabolism, leading to reduction in clearance of the compound from the body and hence increased exposure to the compound, or a favourable metabolic profile may mean, for example, not forming active metabolites (which might be considered undesirable in some circumstances).

For example, compounds of Aspects A to F may have favourable toxicological profiles.

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

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

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

gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

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

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

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

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

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

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

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

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

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active

agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula (I), (IA), (IB), (IC) or (ID) will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula (I), (IA), (IB), (IC) or (ID) for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

The elevation of GLK activity described herein may be applied as a sole therapy or in combination with one or more other substances and/or treatments for the indication being treated. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For example in the treatment of diabetes mellitus, chemotherapy may include the following main categories of treatment:

1) Insulin and insulin analogues;

2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide);

3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, and GLP-1 agonists);

4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone), and agents with combined PPARalpha and gamma activity;

5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen phopsphorylase inhibitors, glycogen synthase kinase inhibitors);

6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);

7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors);

8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors);

9) Anti-obesity agents (for example sibutramine and orlistat);

10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (eg statins); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);

12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;

13) Agents which antagonise the actions of glucagon; and

14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

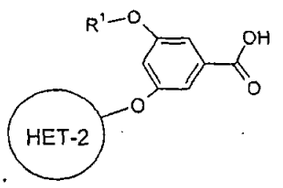
According to another aspect of the present invention there is provided individual compounds produced as end products in the Examples set out below and salts thereof.

A compound of the invention, or a salt thereof, may be prepared by any process known to be applicable to the preparation of such compounds or structurally related compounds. Functional groups may be protected and deprotected using conventional methods. For examples of protecting groups such as amino and carboxylic acid protecting

groups (as well as means of formation and eventual deprotection), see T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Processes for the synthesis of compounds of Formula (I), (IA), (IB), (IC) or (ID) are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), (IA), (IB), (IC) or (ID), which comprises a process a) to e) (wherein the variables are as defined hereinbefore for compounds of Formula (I), (IA), (IB), (IC) or (ID) unless otherwise defined):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is as hereinbefore defined or a protected version thereof;



(III)



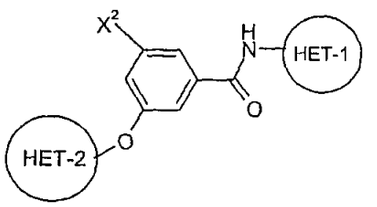
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



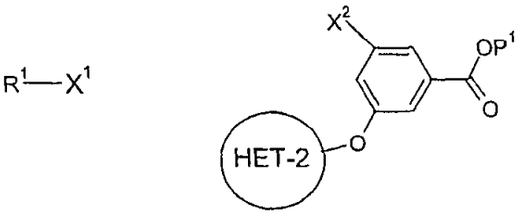
(V)



(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is as hereinbefore defined or a protected version thereof;

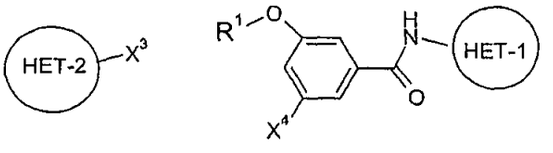
process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(V) (VII)

or

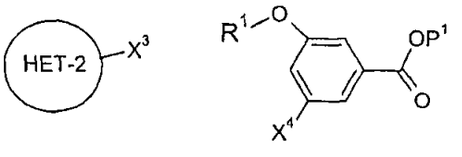
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



(VIII) (IX)

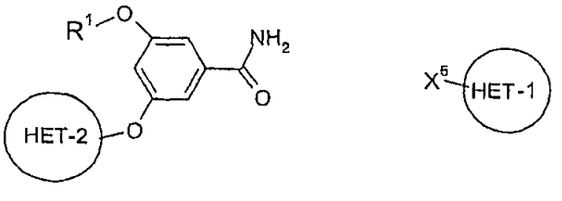
wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is as hereinbefore defined or a protected version thereof;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(VIII) (X)

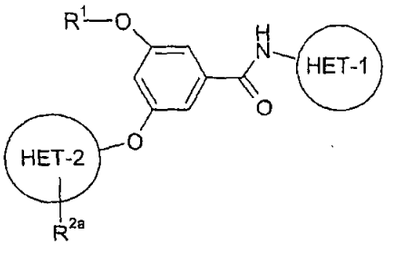
(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



(XI) (XII);

wherein X^5 is a leaving group; and wherein R^1 is as hereinbefore defined or a protected version thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt thereof.

Suitable leaving groups X^1 to X^5 for processes b) to d) are any leaving group known in the art for these types of reactions, for example halo, alkoxy, trifluoromethanesulfonyloxy, methanesulfonyloxy, or p-toluenesulfonyloxy; or a group (such as a hydroxy group) that may be converted into a leaving group (such as an oxytriphenylphosphonium group) *in situ*.

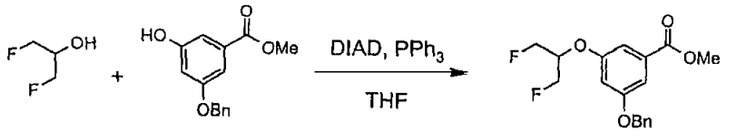
Suitable values for R^1 containing a protected hydroxy group are any suitable protected hydroxy group known in the art, for example simple ethers such as a methyl ether, tert-butyl ether or silylethers such as $-OSi[(1\text{-}4C)alkyl]_3$ (wherein each (1-4C)alkyl group is independently selected from methyl, ethyl, propyl, isopropyl, and tertbutyl). Examples of such trialkylsilyl groups are trimethylsilyl, triethylsilyl, triisopropylsilyl and tert-butyldimethylsilyl. Further suitable silyl ethers are those containing phenyl and substituted phenyl groups, such as $-Si(PhMe_2)$ and $-Si(TolMe_2)$ (wherein Tol = methylbenzene). Further suitable values for hydroxy protecting groups are given hereinafter.

Compounds of Formulae (III) to (XII) are commercially available, or are known in the art, or may be made by processes known in the art, for example as shown in the accompanying

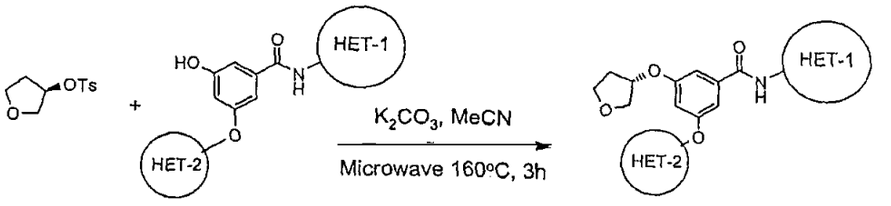
Examples, or as described below. For further information on processes for making such compounds, we refer to our PCT publications WO 03/000267, WO 03/015774 and WO 03/000262 and references therein. In general it will be appreciated that any aryl-O or alkyl-O bond may be formed by nucleophilic substitution or metal catalysed processes, optionally in the presence of a suitable base.

Compounds of Formula (XIII) may be made by processes such as those shown in processes a) to d) and/or by those processes mentioned above for compounds of formulae (III) to (XII).

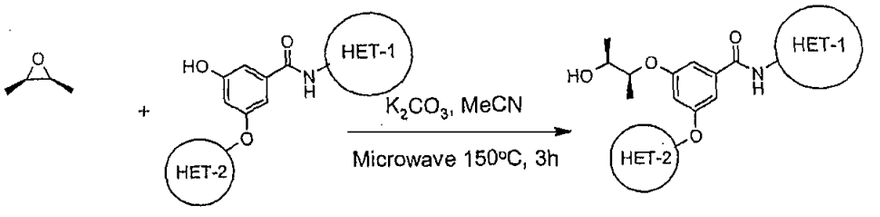
The group R^1 in the compounds of formulae (III), (IX), (X), (XI) and (XIII) may be made by reaction of suitable precursors with compounds of formula (V) or derivatives thereof, depending on the nature of the R^1 group, for example, by nucleophilic displacement of a leaving group X^1 in a compound of formula (V). Compounds of formula (V) are generally commercially available or maybe made by simple functional group interconversions from comercially available compounds, or by literature methods. Further information is available in WO2004/076420, WO2005/054200, WO2005/054233, WO 2005/044801 and WO 2005/056530. Some illustrative examples using various R^1 groups are given in the Schemes below, and/or in the accompanying examples, and may generally be applied analogously to R^1 groups not shown below by methods known in the art, see for example Bull. Chem. Soc. Japan, 73 (2000), 471-484, International Patent Application WO 2002/050003 and Bioorganic and Medicinal Chemistry Letters, (2001), *11*, 407.



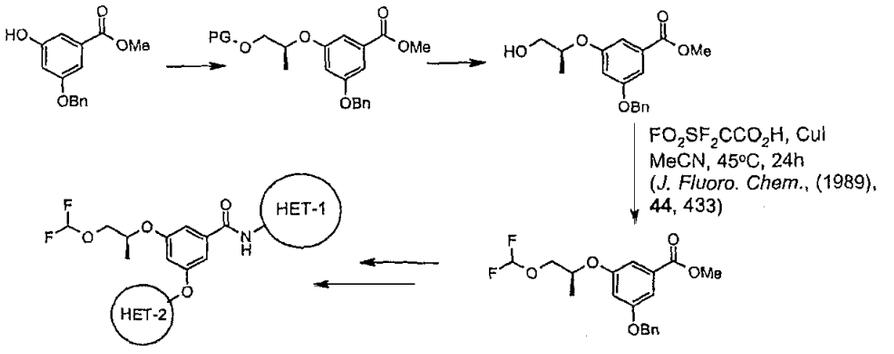
Scheme 1



Scheme 2



Scheme 3



Scheme 4

[PG is protecting group, Ts is p-toluenesulfonyl].

Examples of conversions of a compound of Formula (I) into another compound of Formula (I), well known to those skilled in the art, include functional group interconversions such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions. Further examples of a conversion of a compound of Formula (I) into another compound of Formula (I) is methylation of a hydroxy group in R^1 to give a methoxy group, and conversion of, for example, a hydroxymethyl group in R^1 (such as when R^1 is hydroxyprop-2-yl) into a difluoromethoxy group, using reactions such as those as illustrated in Scheme 4.

It will be understood that substituents R^3, R^6 and/or R^7 may be introduced into the molecule at any convenient point in the synthetic sequence or may be present in the starting materials. A precursor to one of these substituents may be present in the molecule during the process steps a) to e) above, and then be transformed into the desired substituent as a final step to form the compound of formula (I); followed where necessary by

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt thereof.

Specific reaction conditions for the above reactions are as follows, wherein when P^1 is a protecting group P^1 is preferably (1-4C)alkyl, for example methyl or ethyl:

Process a) – coupling reactions of amino groups with carboxylic acids to form an amide are well known in the art. For example,

(i) using an appropriate coupling reaction, such as a carbodiimide coupling reaction performed with EDAC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in the presence of dimethylaminopyridine (DMAP) in a suitable solvent such as dichloromethane (DCM), chloroform or dimethylformamide (DMF) at room temperature; or

(ii) reaction in which the carboxylic group is activated to an acid chloride by reaction with oxalyl chloride in the presence of a suitable solvent such as DCM. The acid chloride can then be reacted with a compound of Formula (IV) in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between 0°C and 80°C.

Process b) – compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as DMF or tetrahydrofuran (THF), with a base such as sodium hydride or potassium *tert*-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; alternatively, compounds of Formula (V) and (VI) can be reacted together in a suitable solvent, such as THF or DCM, with a suitable phosphine such as triphenylphosphine, and azodicarboxylate such as diethylazodicarboxylate; process b) could also be carried out using a precursor to the ester of formula (VII) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

Process c) - compounds of Formula (VIII) and (IX) can be reacted together in a suitable solvent, such as DMF or THF, with a base such as sodium hydride or potassium tert-butoxide, at a temperature in the range 0 to 200°C, optionally using microwave heating or metal catalysis such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide; process c) could also be carried out using a precursor to the ester of

formula (X) such as an aryl-nitrile or trifluoromethyl derivative, followed by conversion to a carboxylic acid and amide formation as previously described;

compounds of the formula (VIII) are commercially available or can be prepared from commercially available materials by processes well known to those skilled in the art, for example functional group interconversions (such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction), and/or further functionalisation and/or cyclisation by standard reactions (such as amide or sulphonamide or metal-catalysed coupling, or nucleophilic displacement or electrophilic substitution reactions);

Process d) – reaction of a compound of Formula (XI) with a compound of Formula (XII) can be performed in a polar solvent, such as DMF or a non-polar solvent such as THF with a strong base, such as sodium hydride or potassium *tert*-butoxide at a temperature between 0 and 200°C, optionally using microwave heating or metal catalysis, such as palladium(II)acetate, palladium on carbon, copper(II)acetate or copper(I)iodide;

Process e) - coupling reactions of amino groups with carboxylic or sulfonic acids or acid derivatives to form an amide are well known in the art and are described above for Process a).

Certain intermediates of formula (III), (VI), (VII), (IX) and/or (XI) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (III), (IX) and/or (XI) wherein R^1 is as defined herein for a compound of formula (I) are believed to be novel and comprise an independent aspect of the invention.

Certain intermediates of formula (XIII) are believed to be novel and comprise an independent aspect of the invention.

During the preparation process, it may be advantageous to use a protecting group for a functional group within the molecule. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific

examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (e.g. isopropyl, t-butyl); lower alkoxy lower alkyl groups (e.g. methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (e.g. 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (e.g. p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (e.g. trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (e.g. trimethylsilylethyl); and (2-6C)alkenyl groups (e.g. allyl and vinylethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, metal- or enzymically-catalysed hydrolysis. Hydrogenation may also be used.

Examples of hydroxy protecting groups include methyl, t-butyl, lower alkenyl groups (e.g. allyl); lower alkanoyl groups (e.g. acetyl); lower alkoxycarbonyl groups (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl groups (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkyl/arylsilyl groups (e.g. trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl); tetrahydropyran-2-yl; aryl lower alkyl groups (e.g. benzyl) groups; and triaryl lower alkyl groups (e.g. triphenylmethyl). Examples of amino protecting groups include formyl, aralkyl groups (e.g. benzyl and substituted benzyl, e.g. p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (e.g. t-butoxycarbonyl); lower alkenyloxycarbonyl (e.g. allyloxycarbonyl); aryl lower alkoxycarbonyl groups (e.g. benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (e.g. trimethylsilyl and t-butyldimethylsilyl); alkylidene (e.g. methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, hydrogenation, nucleophilic displacement, acid-, base, metal- or enzymically-catalysed hydrolysis, catalytic hydrogenolysis or photolytically for groups such as o-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups. For example, methylether protecting groups for hydroxy groups may be removed by trimethylsilyliodide. A tert-butyl ether protecting group for a hydroxy group may be removed by hydrolysis, for example by use of hydrochloric acid in methanol.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilylethoxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, t-butyldimethylsily, t-butyldiphenylsilyl); tri alkyl/arylsilyloxymethyl (e.g. t-butyldimethylsilyloxymethyl, t-butyldiphenylsilyloxymethyl); 4-alkoxyphenyl (e.g. 4-methoxyphenyl); 2,4-di(alkoxy)phenyl (e.g. 2,4-dimethoxyphenyl); 4-alkoxybenzyl (e.g. 4-methoxybenzyl); 2,4-di(alkoxy)benzyl (e.g. 2,4-di(methoxy)benzyl); and alk-1-enyl (e.g. allyl, but-1-enyl and substituted vinyl e.g. 2-phenylvinyl).

Aralkoxymethyl, groups may be introduced onto the amide group by reacting the latter group with the appropriate aralkoxymethyl chloride, and removed by catalytic hydrogenation. Alkoxymethyl, tri alkyl/arylsilyl and tri alkyl/silyloxymethyl groups may be introduced by reacting the amide with the appropriate chloride and removing with acid; or in the case of the silyl containing groups, fluoride ions. The alkoxyphenyl and alkoxybenzyl groups are conveniently introduced by arylation or alkylation with an appropriate halide and removed by oxidation with ceric ammonium nitrate. Finally alk-1-enyl groups may be introduced by reacting the amide with the appropriate aldehyde and removed with acid.

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

The following examples are for illustration purposes and are not intended to limit the scope of this application. Each exemplified compound represents a particular and independent aspect of the invention. In the following non-limiting Examples, unless otherwise stated:

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

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

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

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) with a field strength (for proton) of 300MHz (generally using a Varian Gemini 2000) or 400 MHz (generally using a Bruker Avance DPX400), unless otherwise stated, and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) Purification by chromatography generally refers to flash column chromatography, on silica unless otherwise stated. Column chromatography was generally carried out using prepacked silica cartridges (from 4g up to 400g) such as Redisep™ (available, for example, from Presearch Ltd, Hitchin, Herts, UK) or Biotage (Biotage UK Ltd, Hertford, Herts, UK), eluted using a pump and fraction collector system. Purification by Solid Phase Extraction (SPE) methods generally refers to the use of chromatography cartridges packed with SPE materials such as ISOLUTE® SCX-2 columns (available, for example, From International Sorbent Technology Ltd, Dryffryn Business Park, Hengoed, Mid Glamorgan, UK);

(vii) Mass spectra (MS) data was generated on an LCMS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phemonenex Gemini C18 5μm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture; or using an equivalent solvent system with methanol instead of acetonitrile), or basic eluent

(for example, using a gradient between 0 – 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ spectrometer. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

(viii) Suitable microwave reactors include "Smith Creator", "CEM Explorer", "Biotage Initiator sixty" and "Biotage Initiator eight".

(ix) Melting points were generally carried out by Differential Scanning Calorimetry (DSC); analysis was generally conducted using equipment such as a Mettler DSC822e or a Mettler DSC820. Samples of typically less than 5 mg of material, contained in a 40 µL aluminum pan fitted with a pierced lid, were heated over the temperature range 25°C to 325°C at a constant heating rate of 10°C per minute. A purge gas using nitrogen was used at a flow rate of 100 mL per minute. It will be understood that the onset and/or peak temperature values of the DSC may vary slightly from one machine to another, one method to another or from one sample to another, and so the values quoted are not to be construed as absolute. It will be appreciated that some samples may be solvates and that this may also affect melting points.

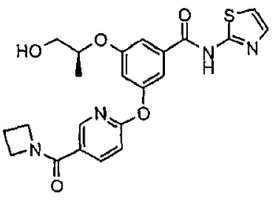
Abbreviations

DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIAD	diisopropylazodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMA	dimethylacetamide
DMSO	dimethyl sulphoxide
DMF	*dimethylformamide*
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexofluorophosphate
HPLC	high pressure liquid chromatography

HPMC	Hydroxypropylmethylcellulose
LCMS	liquid chromatography / mass spectroscopy
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
RT	room temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
$CDCl_3$	deuterochloroform
$MgSO_4$	magnesium sulfate
NaHMDS	sodium hexamethyldisilazide

All compound names were derived using ACD NAME computer package.

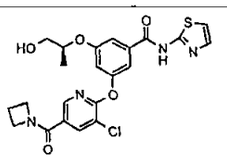
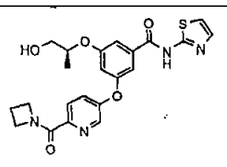
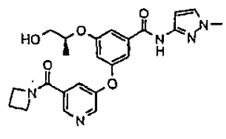
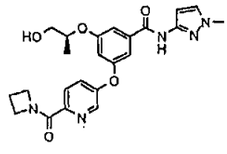
Example 1: 3-{[5-(Azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide



A mixture of 3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (0.15 g, 0.33 mmol) in methanol (10 mL) and 1M hydrochloric acid (10 mL) was stirred for 90 mins at RT. The volatiles were removed *in vacuo* and the residue taken to pH6 with saturated aqueous sodium bicarbonate solution then extracted into ethyl acetate (3 x 30 mL) and the combined organic layers washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvents removed *in vacuo* to a residue which was chromatographed on silica eluting with a gradient of 0-10% methanol in ethyl acetate to give the desired compound (65 mg).

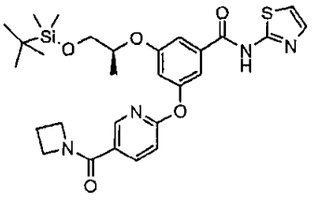
^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.30 (s, 1H), 2.39 (quin, 2H), 3.79 (m, 2H), 4.20-4.40 (brm, 4H), 4.58 (m, 1H), 6.98 (m, 2H), 7.27 (m, 1H), 7.35 (m, 1H), 7.39 (s, 1H), 7.41 (s, 1H), 8.11 (d, 1H), 8.41 (s, 1H), 11.50 (s, 1H). *m/z* 455 $(M+H)^+$

The following compounds were synthesised in an analogous fashion from the appropriate silyl ether.

Example	Structure	m/z	NMR
1a		489, 491 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 3H), 2.25 (s, 1H), 2.43 (quin, 2H), 3.77 (m, 2H), 4.20-4.40 (brm, 4H), 4.59 (m, 1H), 6.95 (d, 1H), 7.03 (s, 1H), 7.31 (d, 1H), 7.39 (s, 1H), 7.47 (s, 1H), 8.17 (s, 1H), 8.27 (s, 1H), 11.60 (brs, 1H).
1b		455 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.22 (d, 3H), 2.38 (m, 3H), 3.68 (m, 2H), 4.19 (t, 2H), 4.48 (m, 1H), 4.63 (t, 2H), 6.75 (m, 1H), 6.91 (d, 1H), 7.13 (s, 1H), 7.19 (m, 1H), 7.28 (m, 2H), 8.03 (d, 1H), 8.22 (s, 1H), 11.40 (brs, 1H).
1c		452 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.40 (quin, 2H), 3.78 (m, 2H), 3.82 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.57 (sextet, 1H), 6.80 (d, 2H), 7.11 (s, 1H), 7.28 (m, 2H), 7.63 (s, 1H), 8.52 (s, 1H), 8.61 (s, 2H)
1d		452 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.26 (quin, 2H), 2.48 (t, 1H), 3.67 (m, 2H), 3.69 (s, 3H), 4.18 (t, 2H), 4.45 (sextet, 1H), 4.63 (t, 2H), 6.70 9m, 2H), 7.05 (m, 1H), 7.20 (m, 2H), 7.28 (m, 1H), 8.02 (d, 1H), 8.21 (d, 1H), 8.73 (s, 1H)

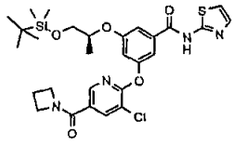
The preparation of 3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide used in **Example 1** is described below:

3-{[5-(Azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide



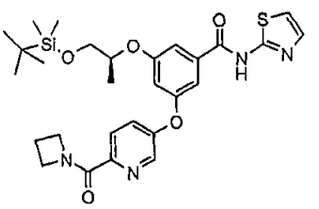
Potassium carbonate (0.14 g, 0.98 mmol) was added to a mixture of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-1,3-thiazol-2-ylbenzamide (200 mg, 0.49 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (96 mg, 0.49 mmol) in acetonitrile (5.0 mL) and the stirred mixture heated at 160°C in a 'Biotage initiator Microwave' for 4 hours. The mixture was allowed to reach RT and pressure and was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was separated, washed with water (5 x 50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with a gradient of 60-100% ethyl acetate in isohexane, to give the desired compound. (0.15 g).
m/z 569 $(M+H)^+$

The precursor for **Example 1a** was prepared in a similar fashion from 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-1,3-thiazol-2-ylbenzamide using 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine:

Structure	m/z	NMR
	603, 605 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9H), 1.27 (d, 3H), 2.32 (quin, 2H), 3.60-3.80 (m, 2H), 4.15-4.35 (brm, 4H), 4.45 (m, 1H), 6.83 (d, 1H), 6.95 (m, 1H), 7.19 (d, 1H), 7.25 (s, 1H), 7.30 (s, 1H), 8.08 (d, 1H), 8.17 (d, 1H), 11.95 (brs, 1H).

The precursor for **Example 1b** was prepared as described below:

3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide

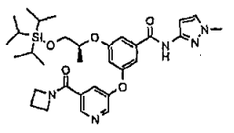
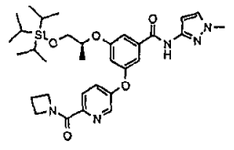


Cesium carbonate (0.478 g, 1.47 mmol) was added to a mixture of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-1,3-thiazol-2-ylbenzamide (200 mg, 0.49 mmol), bromotris(triphenylphosphine)copper (46 mg, 0.049 mmol) and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (130 mg, 5.39 mmol) in DMA (5.0 mL) and the stirred mixture heated at 160°C in a 'Biotage initiator Microwave' for 3 hours. The mixture was allowed to reach RT and pressure and was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was separated, washed with water (5 x 50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give the desired compound. (47 mg).

^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.29 (d, 3H), 2.32 (quin, 2H), 3.65-3.80 (m, 2H), 4.21 (t, 2H), 4.46 (m, 1H), 4.68 (t, 2H), 6.81 (s, 1H), 6.92 (m, 1H), 7.25 (m, 1H), 7.30-7.50 (m, 2H), 7.65 (m, 1H), 8.08 (d, 1H), 8.28 (s, 1H), 11.50 (brs, 1H).

m/z 569 $(M+H)^+$

The precursors for examples **1c-1d** were prepared in a similar fashion from 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[((1*S*)-1-methyl-2-{[tris(1-methylethyl)silyl]oxy}ethyl)oxy]benzamide using the appropriate bromopyridine:

Structure	m/z	NMR
	608 $(M+H)^+$	
	608 $(M+H)^+$	

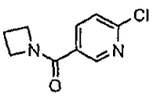
Bromotris(triphenylphosphine)copper may be prepared according to Synthetic Communications, 31(18), 2865-2879 (2001). The preparation of bromotris(triphenylphosphine)copper is described below.

Bromotris(triphenylphosphine)copper

Copper (II) bromide (111.7 g, 0.5 mol) was added in portions to a stirred solution of triphenylphosphine (557.4 g, 2.13 mol) in methanol (1.85 L) at RT (an exotherm to 32°C was observed). The reaction was stirred for 10 minutes then heated to 65°C and cooled overnight. The solid was collected by filtration, washed with ethanol (5 vol), diethyl ether (3 x 5 vol), dried on sinter under vacuum for 2 hours, then in a vacuum oven at 30°C overnight to give product as crystalline solid (460 g).

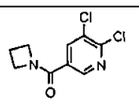
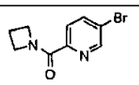
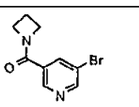
The preparation of 5-(azetidin-1-ylcarbonyl)-2-chloropyridine used in the preparation of 3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide, a precursor to **Example 1**, is described below:

5-(Azetidin-1-ylcarbonyl)-2-chloropyridine



DMF (2 drops) was added to a solution of 6-chloronicotinic acid (1.00 g, 6.35 mmol) and oxalyl chloride (0.67 mL, 7.62 mmol) in DCM (20 mL) and 2M hydrogen chloride in ether (3.15 mL, 6.35 mmol). The mixture was stirred at RT for 4 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride was dissolved in DCM (10 mL) and added to a mixture of azetidine hydrochloride (0.66 g, 6.99 mmol) and triethylamine (2.14 mL, 13.97 mmol) in DCM (10 mL) then stirred at RT for 24 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (100 mL) and 1M citric acid (50 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), and the solvent removed *in vacuo* to give a residue which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (0.73 g). ^{1}H NMR δ ($CDCl_3$) 2.43 (quin, 2H), 4.2-4.4 (brm, 4H), 7.42 (d, 1H), 7.97 (d, 1H), 8.63 (s, 1H). *m/z* 197 $(M+H)^+$

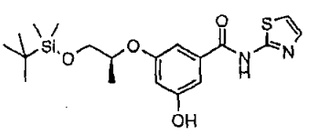
The halopyridines used in the preparation of precursors for **Examples 1a-1d** were prepared in a similar fashion from the appropriate nicotinic acid:

Structure	m/z	NMR
		^{1}H NMR δ ($CDCl_3$): 2.43 (quin, 2H), 4.21 - 4.44 (m, 4H), 8.11 (d, 1H), 8.53 (d, 1H)
	241,243 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.35(quin, 2H), 4.25 (t, 2H), 4.70 (t, 2H), 7.93 (d, 1H), 8.03 (d, 1H), 8.63 (s, 1H).
	241,243 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.42 (quin, 2H), 4.20 - 4.45 (m, 4H), 8.16 (t, 1H), 8.76 (t, 2H)

The nicotinic acids were either commercially available compounds or compounds known in the literature. Reference for 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (Heterocycles, 15(1) **1981**, 213-23).

The preparation of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-1,3-thiazol-2-ylbenzamide used in the synthesis of **Example 1, 1a** and **1b** is described below:

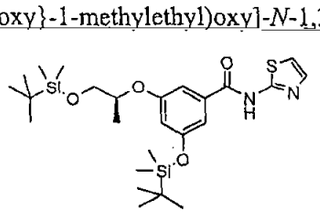
3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-1,3-thiazol-2-ylbenzamide



An aqueous solution of lithium hydroxide monohydrate (0.304 g, 7.25 mmol) was added to a solution of 3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (1.552 g, 2.90 mmol) in THF (40 mL) and stirred at RT overnight. The THF was removed *in vacuo* and the residual solution adjusted to pH 7 by addition of 1N hydrochloric acid (7.25 mL). A gum formed, and the solution was filtered and the gum dissolved in methanol. The filtrate was partitioned with ethyl acetate (75 mL) and the organics washed with brine, dried ($MgSO_4$), combined with the methanol solution and evaporated to a residue which was chromatographed on silica, eluting with 40% ethyl acetate in isohexane, to give the required product (0.865 g)

^{1}H NMR δ ($CDCl_3$): -0.02 (d, 6H), 0.81 (s, 9H), 1.24 (d, 3H), 3.67 (m, 2H), 4.43 (sextet, 1H), 6.65 (t, 1H), 7.00 (d, 1H), 7.13 (t, 1H), 7.15 (t, 1H), 7.40 (d, 1H). *m/z* 409 $(M+H)^+$

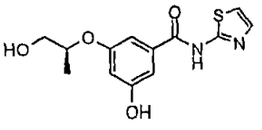
3-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide



tert-Butyldimethylsilyl chloride (1.66 g, 11.0 mmol) and imidazole (1.78 g, 26.0 mmol) were a to a solution of 3-hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide (1.541 g, 5.24 mmol)in DMF (10 mL) and the reaction stirred at RT under a

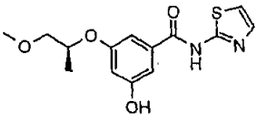
silica drying tube overnight. Water (30 mL) was added and the solution partitioned with ethyl acetate (100 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 15% ethyl acetate in isohexane, to give the required product (1.525 g). ^{1}H NMR δ ($CDCl_3$): -0.17 (d, 6H), 0.00 (s, 6H), 0.65 (s, 9H), 0.76 (s, 9H), 1.08 (d, 3H), 3.50 (m, 2H), 4.25 (sextet, 1H), 6.43 (t, 1H), 6.77 (d, 1H), 6.83 (t, 1H), 6.96 (t, 1H), 7.06 (d, 1H). *m/z* 423 $(M-H)^-$

3-Hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide



Iodo(trimethyl)silane (7.19 mL, 50.5 mmol) was added dropwise to a solution of 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide (3.116 g, 10.1 mmol) in acetonitrile (60 mL) under an inert atmosphere and the reaction stirred at RT overnight. Methanol (5 mL) was added and the reaction stirred a further 10 minutes. Saturated sodium thiosulphate solution (5 mL) and saturated potassium carbonate solution (5 mL) were added and the reaction stirred a further 10 minutes. The organic solvents were removed *in vacuo* and the resulting solution partitioned extracted with ethyl acetate (100 mL). The Aqueous layer was adjusted to pH 5 with the addition of 1M hydrochloric acid and extracted with ethyl acetate. The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (1.541 g).
^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.52 (m, 2H), 4.50 (sextet, 1H), 6.55 (t, 1H), 7.04 (t, 1H), 7.18 (t, 1H), 7.27 (d, 1H), 7.55 (d, 1H), 12.47 (s, 1H). *m/z* 295 $(M+H)^+$

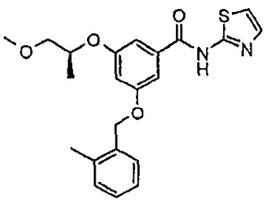
3-Hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide



A solution of 3-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-5-{[(2-methylphenyl)methyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide (6.9 g) and thioanisole (10 mL) in trifluoroacetic acid (65

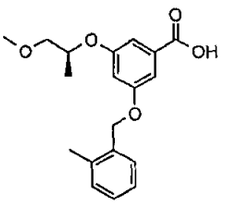
mL) was stirred at ambient temperature for 16 hours. The trifluoroacetic acid was removed *in vacuo* and the residual oil partitioned between ethyl acetate (75 mL) and aqueous sodium hydrogen carbonate solution (200 mL). The aqueous layer was separated, extracted with ethyl acetate (2 x 75 mL), and the combined organic extracts washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 50% ethyl acetate in isohexane as eluant to give the desired compound (4.6 g).
^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.5-4.6 (m, 1H), 6.65 (s, 1H), 6.95 (d, 1H), 7.05 (s, 1H), 7.1 (s, 1H), 7.25 (d, 1H). *m/z* 309 $(M+H)^+$

3-{[(1*S*)-2-Methoxy-(1-methylethyl)oxy}-5-{[(2-methylphenyl)methyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide



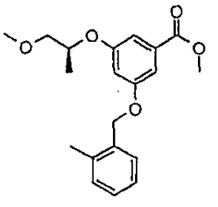
To a solution of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl)methyl]oxy} benzoic acid (9.55 g) in DCM (140 mL) was added oxalyl chloride (2.83 mL), followed by DMF (1 drop), and the mixture stirred at ambient temperature for 16 hours. The DCM and excess oxalyl chloride were removed *in vacuo*, the residual oil dissolved in DCM (25 mL) and added to a solution of 2-aminothiazole (2.84g) and triethylamine (7.88 mL) in DCM (75 mL) at 0-5°C, and the mixture stirred at ambient temperature for 4 hours. The DCM and excess triethylamine were removed *in vacuo*, the residual oil partitioned between ethyl acetate (100 mL) and 1M hydrochloric acid (100 mL). The ethyl acetate layer was separated, washed sequentially with 1M hydrochloric acid, aqueous sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on alumina with ethyl acetate as eluant to give the desired compound (11.0 g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.35 (s,3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.55-4.6 (m, 1H), 5.0 (s,2H), 6.8 (s, 1H), 6.95 (d, 1H), 7.15 (s, 1H), 7.25 (m, 5H), 7.4 (d, 1H). *m/z* 413 $(M+H)^+$

3-[(1*S*)-2-Methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl)methyl]oxy}benzoic acid



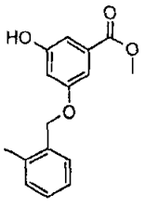
A solution of methyl 3-[{(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl) methyl] oxy}benzoate (10.65g) in THF (200 mL) and methanol (50 mL) was added to a solution of lithium hydroxide monohydrate (6.0g) in water (100 mL). The mixture was stirred at ambient temperature for 16 hours and the THF and methanol removed *in vacuo*. The aqueous layer was acidified to pH1 with hydrochloric acid, and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give the desired compound (9.55 g). *m/z* 329 $(M-H)^-$

Methyl 3-[{(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[(2-methylphenyl)methyl]oxy} benzoate



A stirred suspension of methyl 3-hydroxy-5-{[(2-methylphenyl)methyl]oxy}benzoate (15.3 g) and polymer-supported triphenyl phosphine (39.2 g) in dry DCM (900 mL) was cooled in an ice-bath and diisopropyl azodicarboxylate (11.88 mL) was added drop wise. The reaction mixture was stirred at 0-5°C for 30 minutes and (*R*)-1-methoxy-propan-2-ol was added dropwise. The reaction mixture was stirred at ambient temperature for 16 hours, filtered through diatomaceous earth and the DCM evaporated to a residue which was chromatographed on silica with 10% ethyl acetate in isohexane as eluant to give the desired compound (10.7 g). ^1H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.4 (s,3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 3.9 (s, 3H), 4.55-4.6 (m, 1H), 5.0 (s,2H), 6.8 (s, 1H), 7.25 (m, 5H), 7.4 (d, 1H)

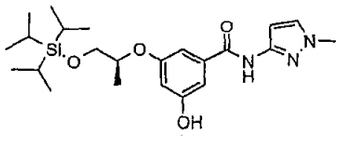
Methyl 3-hydroxy-5-{[(2-methylphenyl)methyl]oxy}benzoate



To a solution of methyl 3,5-dihydroxybenzoate (50 g, 0.30 mol) in DMF (500 mL) at 0°C was added sodium hydride (10.8 g, 0.27 mol) portionwise, maintaining the reaction temperature below 10°C. The reaction was allowed to warm to 15°C, and was stirred for 20 minutes. The mixture was cooled to 0°C and a solution of 2-methylbenzyl bromide (36 mL, 0.27 mol) in DMF (50 mL) was added over 30 minutes. The reaction was warmed to ambient temperature and concentrated *in vacuo*, the residual oil partitioned between ethyl acetate (500 mL) and water (250 mL), the ethyl acetate layer separated, washed sequentially with water and brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica eluting with a gradient of 0-100% ethyl acetate in isohexane to give the desired compound (21.9 g). ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3H), 3.90 (s, 3H), 5.02 (s, 2H), 5.61 (s, 1H), 6.69 (t, 1H), 7.15-7.42 (m, 6H).

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[((1*S*)-1-methyl-2-{[tris(1-methylethyl)silyl]oxy}ethyl)oxy]benzamide used in the synthesis of **Example 1c-1d** is described below:

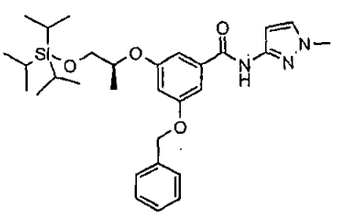
3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[((1*S*)-1-methyl-2-{[tris(1-methylethyl)silyl]oxy}ethyl)oxy]benzamide



10% Palladium on carbon was added to 3-(benzyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethoxy}benzamide (21.7 g, 40.4 mmol) in dry THF (480 mL) under argon. The reaction mixture was degassed and placed under a hydrogen balloon and stirred for 16 hours. The atmosphere was replaced with argon and

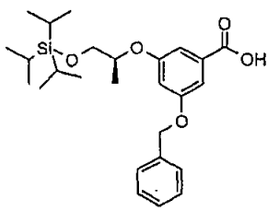
mixture was filtered through diatomaceous earth then the filtrate evaporated and dried under high vacuum for 1 hour to give the title compound (18.2 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.3 (d, 3H), 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 4.5 (m, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.20 (s, 1H), 7.3 (s, 1H), 8.7 (s, 1H). *m/z* 448 $(M+H)^+$, 446 $(M-H)^-$

3-(Benzyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethoxy}benzamide



HATU (23.5 g, 61.8 mmol) was added to 3-(benzyloxy)-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethoxy}benzoic acid (23.6 g, 51.5 mmol), followed by addition of DMF (140 mL), and cooled to 0°C. 3-Amino-1-methylpyrazole (6.00 g. 61.8 mmol) was added followed by DIPEA (21.3 mL) and the reaction was stirred under argon at 0°C for 3 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate (500 mL) and washed with citric acid solution (200 mL), sodium hydrogen carbonate solution (150 mL), and saturated brine solution (2 x 150mL). The organic layer was separated and dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography, eluting with 1:4 to 1:1 ethyl acetate:hexanes, afforded the title compound as a colourless oil (21.7g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.3 (d, 3H), 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 4.5 (m, 1H), 5.1 (s, 2H), 6.7 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.1 (s, 1H), 7.3 (s, 1H), 7.35 –7.5 (m, 5H), 8.5 (s, 1H). *m/z* 538 $(M+H)^+$

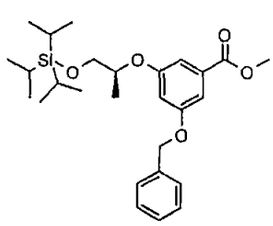
3-(Benzyloxy)-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethoxy}benzoic acid



Lithium hydroxide monohydrate (12.14 g, 0.289 mol) in water (100 mL) was added to a solution of methyl 3-(benzyloxy)-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethoxy}benzoate (62 g, 0.131 mol) in THF (300 mL) and warmed to 43°C. The reaction was stirred for 16 hours, the THF removed *in vacuo* and the resultant mixture acidified to pH 5 with 10% w/v citric acid. This was extracted with ethyl acetate (2 x 300 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to afford the title compound (60.2 g).

^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.35 (d, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 4.5 (m, 1H), 5.1 (s, 2H), 6.8 (s, 1H), 7.3 –7.5 (m, 7H). *m/z* 457 $(M-H)^-$

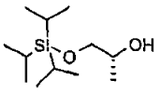
Methyl 3-(benzyloxy)-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethoxy}benzoate



(2*R*)-1-[(Triisopropylsilyl)oxy]propan-2-ol (56.1 g, 242 mmol) was added to a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (50 g, 194 mmol) and triphenylphosphine (63.5 g, 242 mmol) in dry THF (500 mL), at to 0°C, followed by addition of DIAD (47.6 mL, 242 mmol) over 45 minutes under an argon atmosphere. The reaction was stirred at 0°C for 1 hour and allowed to warm up to RT over an hour then stirred at RT for 1 hour. The THF was evaporated and a mixture of ethyl acetate (80 mL) and hexane (120 mL) was added. This mixture stirred for 2 hours and filtered. The precipitate was washed with a mixture of ethyl acetate (20 mL) and hexane (180 mL) and

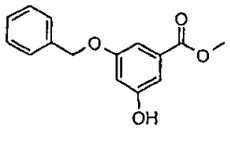
the filtrate evaporated. The residue was purified by column chromatography, eluting with 1:20 to 1:10 ethyl acetate:hexanes, to afford the title compound (65.5 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.35 (d, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 3.9 (s, 3H), 4.5 (m, 1H), 5.05 (s, 2H), 6.75 (s, 1H), 7.2 (s, 1H). 7.3 –7.5 (m, 6H). *m/z* 471 $(M-H)^-$

(2*R*)-1-[(Triisopropylsilyl)oxy]propan-2-ol



Triisopropylsilyl chloride (83.8 mL, 390 mmol) was added slowly over 15 minutes to a solution of (2*R*)-propane-1,2-diol (29.7 g, 390 mmol) in DMF at 0°C (100 mL) keeping the internal temperature below 15°C. This was followed by addition of imidazole (66.4 g, 975 mmol) and the reaction mixture was allowed to warm to RT and stirred under argon for 20 hours. The reaction was quenched with 1M hydrochloric acid/diethyl ether (300 mL/800 mL). The organic layer was separated and washed with 1M hydrochloric acid followed by saturated brine solution. The organic layer was dried ($MgSO_4$), filtered and evaporated. Purification by distillation at 10mmHg, 90-104°C, afforded the title compound as colourless oil (69.5 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.05 (d, 3H), 2.55 (s, 1H), 3.45 (dd, 1H), 3.7 (dd, 1H), 3.85 (m, 1H).

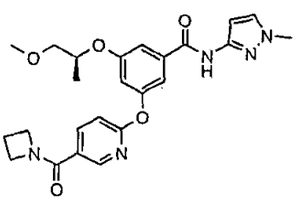
Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate



To a stirred solution of methyl 3,5-dihydroxybenzoate (5.95 mol) in DMF (6 L) was added potassium carbonate (9 mol), and the suspension stirred at ambient temperature under argon. To this was added benzyl bromide (8.42 mol) slowly over 1 hour, with a slight exotherm, and the reaction mixture stirred overnight at ambient temperature. The reaction was quenched cautiously with ammonium chloride solution (5 L) followed by water (35 L). The aqueous suspension was extracted with DCM (1 x 3 L and 2 x 5 L). The combined extracts were washed with water (10 L) and dried overnight ($MgSO_4$). The solution was

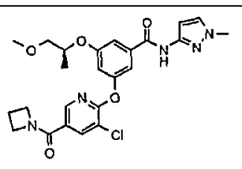
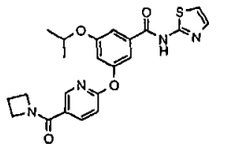
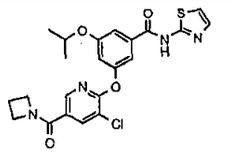
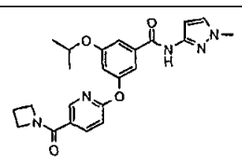
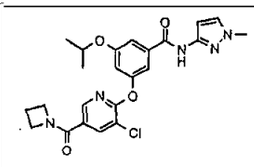
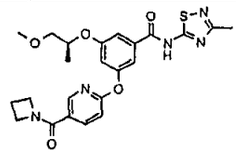
evaporated in *vacuo*; and the crude product chromatographed in 3 batches (flash column, 3 x 2 kg silica, eluting with a gradient consisting of hexane containing 10% DCM, to neat DCM, to DCM containing 50% ethyl acetate) to eliminate starting material. The crude eluant was further chromatographed in 175 g batches (Amicon HPLC, 5 kg normal-phase silica, eluting with isohexane containing 20% v/v of ethyl acetate) to give the desired compound (21% yield). ^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H).

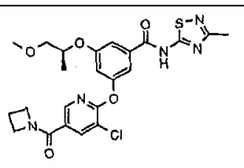
Example 2: 3-{[5-(Azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



Potassium carbonate (0.181 g, 1.31 mmol) was added to a mixture of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.2 g, 0.66 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (129 mg, 0.66 mmol) in acetonitrile (5.0 mL) and the stirred mixture heated at 160°C in a 'Biotage initiator Microwave' for 6 hours. The mixture was allowed to reach RT and pressure and was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was separated, washed with water (5 x 50 mL) brine (50 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the desired compound (202 mg). ^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.38 (quin, 2H), 3.40 (s, 3H), 3.61 - 3.47 (m, 2H), 3.74 (s, 3H), 4.42 - 4.18 (m, 4H), 4.58 (sextet, 1H), 6.80 (d, 1H), 6.91 (t, 1H), 6.97 (d, 1H), 7.21 (t, 1H), 7.26 (d, 1H), 7.33 (t, 1H), 8.09 - 8.05 (m, 1H), 8.42 (d, 1H), 8.92 (s, 1H); *m/z* 466 $(M+H)^+$

In a similar manner, **Examples 2a-2g** were prepared using the appropriate phenol and halopyridine:

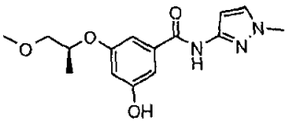
Example	Structure	m/z	NMR
2a		500 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 3H), 2.36 (quintet, 2H), 3.38 (s, 3H), 3.59 - 3.45 (m, 2H), 3.67 (s, 3H), 4.39 - 4.15 (m, 4H), 4.55 (sextet, 1H), 6.79 (d, 1H), 6.92 (t, 1H), 7.20 (t, 1H), 7.25 (d, 1H), 7.35 (t, 1H), 8.14 (d, 1H), 8.20 (d, 1H), 9.42 (s, 1H)
2b		439 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.36 (d, 6H), 2.39 (m, 2H), 4.42 - 4.19 (m, 4H), 4.58 (septet, 1H), 6.90 (d, 1H), 6.93 (t, 1H), 6.98 (d, 1H), 7.22 (d, 1H), 7.34 (t, 1H), 7.40 (m, 1H), 8.08 (m, 1H), 8.41 (d, 1H), 12.21 (s, 1H)
2c		473 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.39 (quintet, 2H), 4.39 - 4.20 (m, 4H), 4.59 (septet, 1H), 6.92 (d, 1H), 6.96 (t, 1H), 7.23 (d, 1H), 7.36 (t, 1H), 7.44 (t, 1H), 8.16 (d, 1H), 8.23 (d, 1H), 12.37 (s, 1H)
2d		436 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.32 (d, 6H), 2.34 (quintet, 2H), 3.71 (s, 3H), 4.37 - 4.17 (m, 4H), 4.54 (septet, 1H), 6.77 (d, 1H), 6.82 (t, 1H), 6.94 (d, 1H), 7.15 (t, 1H), 7.23 (d, 1H), 7.25 (m, 1H), 8.04 (m, 1H), 8.38 (d, 1H), 8.85 (s, 1H)
2e		470 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.40 (quintet, 2H), 3.78 (s, 3H), 4.41 - 4.20 (m, 4H), 4.61 (septet, 1H), 6.81 (d, 1H), 6.89 (t, 1H), 7.20 (t, 1H), 7.29 (m, 1H), 7.32 (t, 1H), 8.17 (d, 1H), 8.25 (d, 1H), 8.72 (s, 1H)
2f		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.39 (quintet, 2H), 2.47 (s, 3H), 3.41 (s, 3H), 3.63 - 3.49 (m, 2H), 4.43 - 4.20 (m, 4H), 4.61 (sextet, 1H), 7.00 (m, 2H), 7.37 (t, 1H), 7.44 (t, 1H), 8.40 (d, 1H), 11.08 (s, 1H)

2g		518 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.40 (quintet, 2H), 2.44 (s, 3H), 3.41 (s, 3H), 3.64 - 3.49 (m, 2H), 4.45 - 4.20 (m, 4H), 4.61 (sextet, 1H), 7.04 (t, 1H), 7.40 (t, 1H), 7.42 (s, 1H), 8.17 (d, 1H), 8.21 (d, 1H), 11.32 (s, 1H)

The preparation of the halopyridines is described in **Example 1**.

The preparation of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide used in the synthesis of **Examples 2** and **2a** is described below:

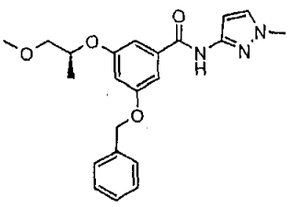
3-Hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



To a solution of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (7.07 g) in THF (50 mL) and methanol (50 mL) was added 10% palladium on carbon (727 mg) as a slurry in THF (1 mL) and methanol (1 mL). The mixture was placed under vacuum and stirred under an atmosphere of hydrogen for 70 hours. The mixture was filtered through diatomaceous earth, and the diatomaceous earth washed with methanol (2 x 100 mL), followed by evaporation *in vacuo*. The residues were dissolved in ethyl acetate (10 mL), treated with isohexane (40 mL), the solid filtered off and washed with isohexane (50 mL) to afford the desired compound (5.17 g) which was used without further purification.

^{1}H NMR δ (d_6-DMSO): 1.22 (d, 3H), 3.28 (s, 3H, obscured by water), 3.38-3.53 (m, 2H), 3.76 (s, 3H), 4.65 (m, 1H), 6.44 (m, 1H), 6.54 (m, 1H), 6.93 (s, 1H), 7.04 (s, 1H), 7.57 (m, 1H), 9.63 (br s, 1H), 10.60 (s, 1H). *m/z* 306 $(M+H)^+$, 304 $(M-H)^-$

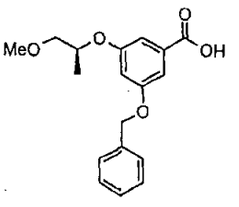
3-[(1*S*)-2-Methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



A solution of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (8.73 g) in DCM (150 mL) was cooled to 0°C. Oxalyl chloride (4.81 mL) and DMF (0.15 mL) were slowly added with stirring. The mixture was allowed to warm to ambient temperature and stirred for 16 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (75 mL). The crude material was dissolved in DCM (75 mL) and slowly added to a stirred suspension of 3-amino-1-methylpyrazole (3.35 g) and DIPEA (14.4 mL) in DCM (75 mL). The mixture was stirred at ambient temperature for 18 hours, before the organics were evaporated *in vacuo* and the residue dissolved in ethyl acetate (150 mL). The organics were washed with 1M aqueous hydrochloric acid (100 mL) and brine (50 mL), and dried ($MgSO_4$), before evaporation *in vacuo* to give crude material. This was chromatographed on a 200g Biotage Flash 75 SiO_2 column (eluting with 30 to 90% ethyl acetate in isohexane), and evaporated *in vacuo* to afford the desired compound (7.07 g).

^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.28 (s, 3H, obscured by water), 3.40-3.52 (m, 2H), 3.77 (s, 3H), 4.70 (m, 1H), 5.03 (s, 2H), 6.56 (m, 1H), 6.71 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.32-7.47 (br m, 5H), 7.58 (m, 1H), 10.73 (s, 1H). *m/z* 396 $(M+H)^+$.

3-[(1*S*)-2-Methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid

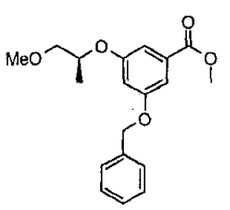


A solution of methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy} benzoate (77.4 mmol) in a mixture of THF (232 mL) and methanol (232 mL) was treated

with a solution of 2M sodium hydroxide (232 mmol), and the reaction mixture stirred for 4 hours at ambient temperature. The resulting solution was diluted with water (250 mL) and most of the organic solvent removed *in vacuo*. The resulting suspension was washed with diethyl ether (3 x 200 mL) and the organic washings discarded. The resulting aqueous solution was acidified to pH4 with 2M hydrochloric acid solution and extracted with ethyl acetate (2 x 200 mL). The extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give the desired compound (99% yield).

^{1}H NMR δ (d_6-DMSO): 1.20 (d, 3H), 3.46 (m, 2H), 4.64 (m, 1H), 5.15 (s, 2H), 6.83 (app t, 1H), 7.06 (s, 1H), 7.13 (s, 1H), 7.30-7.49 (m, 5H), 12.67 (br s, 1H)

Methyl 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoate



To a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (77.4 mmol) in THF was added polymer-supported triphenylphosphine (51.7g of 3 mmol/g loading, 155 mmol) and (*R*)-(-)-1-methoxy-2-propanol (102 mmol). The stirred solution was blanketed with argon and cooled in an ice bath. A solution of DIAD (116 mmol) was added dropwise by syringe over 10 minutes. The solution was stirred for 20 minutes and filtered, washing the residue with THF (500 mL). The filtrate and washings were combined, and evaporated to give the desired compound which was used without further purification.

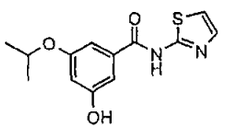
^{1}H NMR δ (d_6-DMSO): 3.26 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 5.14 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.47 (m, 5H)

The ^{1}H NMR spectrum also contained signals consistent with a small amount of bis(1-methylethyl)hydrazine-1,2-dicarboxylate.

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate is described in **Example 1c**.

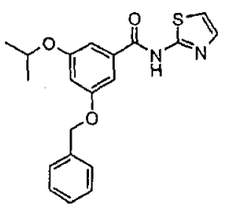
The preparation of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide used in the preparation of **Examples 2b** and **2c** is described below:

3-Hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide



3-[(1-Methylethyl)oxy]-5-[(phenylmethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide (11.2 g) was dissolved in trifluoroacetic acid (60 mL) and treated with thioanisole (17.8 mL). The mixture was left to stir at ambient temperature for 18 hours before the trifluoroacetic acid was removed *in vacuo*. The residues were treated with isohexane (100 mL) and the solid filtered off, before being washed with further isohexane (2 x 20 mL). The solid was dissolved in ethyl acetate (200 mL) and washed with aqueous saturated sodium hydrogen carbonate solution (100 mL). The organics were washed with water (100 mL) and brine (100 mL), and dried ($MgSO_4$) before evaporation *in vacuo* to afford a solid which was washed with isohexane (200 mL) and dried *in vacuo* to give the desired compound (7.18 g). ^{1}H NMR δ (d_6-DMSO): 1.27 (d, 6H), 4.55 (m, 1H), 6.49 (m, 1H), 7.02 (s, 1H), 7.14 (s, 1H), 7.25 (d, 1H), 7.54 (d, 1H), 9.73 (s, 1H), 12.44 (s, 1H). m/z 279 $(M+H)^+$, 277 $(M-H)^-$

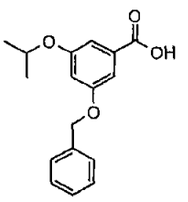
3-[(1-Methylethyl)oxy]-5-[(phenylmethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide



To a solution of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (20 g) in DCM (400 mL), cooled to 0°C was slowly added oxalyl chloride (12.2 mL) and DMF (0.4 mL), with stirring. The mixture was allowed to warm to ambient temperature and stirred for a further 16 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (100 mL). The crude material was dissolved in DCM (200 mL) and slowly added to a stirred suspension of 2-aminothiazole (10.5 g) and diisopropylethylamine (24.3 mL), in DCM (200 mL). The mixture was stirred at ambient temperature for 70 hours, before the organics were removed *in vacuo*. The residues were dissolved in ethyl acetate (300 mL) and washed with 1M aqueous hydrochloric acid (300

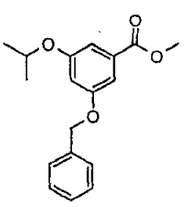
mL). The aqueous layer was extracted with further ethyl acetate (300 mL), and the combined organics washed with brine (75 mL), and dried ($MgSO_4$), before evaporation *in vacuo* to give the desired compound (28 g) which was used without further purification.
^{1}H NMR δ (d_6-DMSO): 1.27 (d, 6H), 4.70 (m, 1H), 5.15 (s, 2H), 6.77 (m, 1H), 7.27 (m, 2H), 7.33-7.47 (brm, 6H), 7.55 (d, 1H). m/z 369 $(M+H)^+$, 367 $(M-H)^-$;
The ^{1}H NMR spectrum also contained signals consistent with a small amount of ethyl acetate.

3-[(1-Methylethyl)oxyl-5-[(phenylmethyl)oxy]benzoic acid



To a solution of methyl 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoate (37 g) in a 1:1 mixture of THF:methanol (300 mL) was added 4M sodium hydroxide solution (150 mL). The mixture was refluxed for 45 minutes, following which the organics were removed *in vacuo*. The aqueous was acidified to pH4 with hydrochloric acid (2M), and extracted with ethyl acetate. The organics were combined, washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (33.5 g), which was used without further purification.
^{1}H NMR δ (d_6-DMSO): 1.26 (d, 6H), 4.59-4.69 (m, 1H), 5.15 (s, 2H), 6.80 (app t, 1H), 7.04 (m, 1H), 7.12 (m, 1H), 7.33 (app t, 1H), 7.40 (t, 2H), 7.46 (d, 2H), 12.95 (s, 1H)

Methyl 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoate

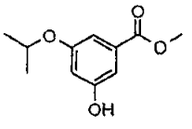


To a solution of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate (25 g) in DMF (250 mL) was added anhydrous potassium carbonate (297 mmol), and benzyl bromide (143

mmol). The mixture was stirred at 60°C for 5 hours, then cooled to room temperature. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organics were combined and washed with further water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give the desired compound (37 g) which was used without further purification.

^{1}H NMR δ (d_6-DMSO): 1.26 (d, 6H), 3.84 (s, 3H), 4.61-4.70 (m, 1H), 5.12 (s, 2H), 6.84 (t, 1H), 7.05 (app t, 1H), 7.12-7.15 (m, 1H), 7.31-7.37 (m, 1H), 7.40 (t, 2H), 7.46 (d, 2H)

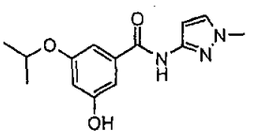
Methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate



To a stirred solution of methyl 3,5-dihydroxybenzoate (0.1 mol) in DMF (180 mL) was added powdered potassium carbonate (0.2 mol) and 2-iodopropane (0.1 mol), and the resulting mixture stirred at ambient temperature for 16 hours. The reaction mixture was poured into water (1000 mL) and the mixture extracted with ether. The extracts were combined and washed sequentially with water (twice) and brine; the solution was dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the crude product as a pale yellow oil (12.6 g). This was treated with toluene (40 mL) and allowed to stand overnight. The insoluble material (starting phenol) was removed by filtration, and the filtrate evaporated *in vacuo*. The resulting oil was chromatographed (2 x 90 g Biotage silica cartridges), eluting with hexane containing ethyl acetate (10% increasing to 15% v/v). The title compound was obtained as an oil (25% yield), which was identical by tlc to a sample prepared by a similar procedure. ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 6H), 3.8 (s, 3H), 4.5 – 4.6 (hept, 1H), 6.55 (m, 1H), 7.85 (m, 1H), 7.95 (m, 1H), 9.8 (s, 1H)

The preparation of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide used in **Example 2d** and **2e** is described below:

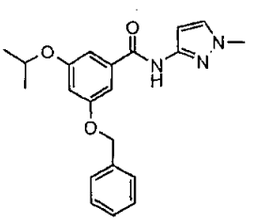
3-Hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-[(1-Methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (51g; 0.14mol) was dissolved in methanol (500 mL) and THF (500 mL) and the flask evacuated and purged with argon (3 times). 10% Palladium on carbon (5.1 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 20 hours. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off through celite, and the filtrate concentrated *in vacuo*. Ethyl acetate was added and filtered to give the desired compound. (30.5 g). A second crop of material was obtained in the same way (4.0 g).

^{1}H NMR δ (d_6-DMSO): 1.30 (d, 6H), 3.78 (s, 3H), 4.68 (sept, 1H), 6.47 (m, 1H), 6.60 (s, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.60 (s, 1H), 10.63 (s, 1H). *m/z* 276 $(M+H)^+$

3-[(1-Methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



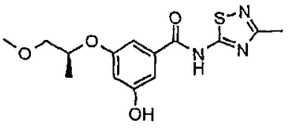
DMF (2 drops) was added to a solution of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (40.0 g, 0.14 mol) and oxalyl chloride (14.6 mL, 0.17 mol) in DCM (700 mL) The mixture was stirred at ambient temperature for 4 hours and the DCM and excess oxalyl chloride evaporated *in vacuo*. The residual acid chloride was dissolved in DCM (300 mL) and added dropwise to 1-methyl-3-aminopyrazole (14.25 g, 0.147 mol) and triethylamine (41 mL, 0.29 mol) in DCM (300 mL), at 0°C. Stirred at ambient temperature for 24 hours. The DCM was evaporated *in vacuo*, and the residue partitioned between ethyl acetate (400 mL) and 1N hydrochloric acid (200 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (200 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was

chromatographed on silica, eluting with a gradient of 50% ethyl acetate in isohexane, to give the desired compound (51 g). ^{1}H NMR δ ($CDCl_3$): 1.30 (d, 6H), 3.61 (s, 3H), 4.50 (sept, 1H), 5.01 (s, 2H), 6.66 (m, 1H), 6.88 (m, 1H), 7.00 (m, 1H), 7.06 (m, 1H), 7.24 (m, 1H), 7.39 (m, 5H), 9.50 (s, 1H). *m/z* 366 $(M+H)^+$

The preparation of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid was described above.

The preparation of 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide used in **Examples 2f** and **2g** is described below:

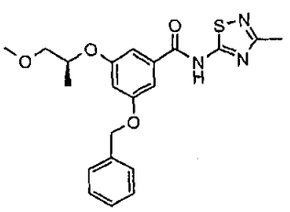
3-Hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide



A solution of 3-{[(1S)-2-methoxy-(1-methylethyl)oxy}-5-{phenylmethyloxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide (9.53 g) and thioanisole (13.9 mL) in trifluoroacetic acid (45 mL) was stirred at ambient temperature for 16 hours. The trifluoroacetic acid was removed *in vacuo* and the residual oil partitioned between ethyl acetate (100 mL) and aqueous sodium hydrogen carbonate solution (300 mL). The aqueous layer was separated, extracted with ethyl acetate (2 x 100 mL), and the combined organic extracts washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica with 50% ethyl acetate in isohexane as eluant to give the desired compound (4.5 g).

^{1}H NMR δ ($CDCl_3$): 1.2 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4-3.6 (m, 2H), 4.6-4.7 (m, 1H), 6.6 (s, 1H), 7.05 (s, 1H), 7.1 (s, 1H), 9.85 (s, 1H), 13.2 (s, 1H). *m/z* 324 $(M+H)^+$

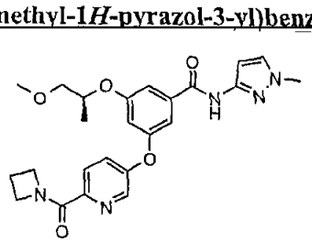
3-{[(1S)-2-Methoxy-(1-methylethyl)oxy}-5-{phenylmethyloxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide



To a solution of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (15.8 g) in DCM (260 mL) was added oxalyl chloride (5.24 mL), followed by DMF (1 drop), and the mixture stirred at ambient temperature for 16 hours. The DCM and excess oxalyl chloride were removed *in vacuo*, the residual oil dissolved in DCM (50 mL) and added to a solution of 5-amino-3-methyl-1,2,4 thiadiazole (6.05 g) and triethylamine (14.6 mL) in DCM (150 mL) at 0-5°C, and the mixture stirred at ambient temperature for 16 hours. The DCM and excess triethylamine were removed *in vacuo*, and the residual oil partitioned between ethyl acetate (250 mL) and 1M hydrochloric acid (150 mL). The ethyl acetate layer was separated, washed sequentially with 1M hydrochloric acid, aqueous sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on alumina with ethyl acetate as eluant, then on silica with 30% ethyl acetate in isohexane as eluant to give the desired compound (9.6 g). ^1H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.45 (s,3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.55-4.6 (m, 1H), 5.05 (s,2H), 6.8 (s, 1H), 7.1 (m, 2H), 7.25 (m, 5H), 10.7 (s, 1H). *m/z* 414 $(M+H)^+$

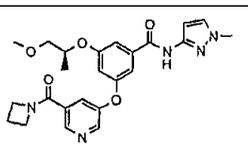
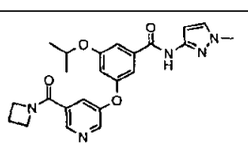
The synthesis of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid is described above.

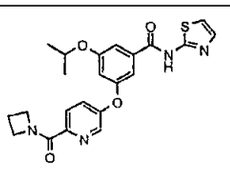
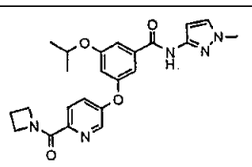
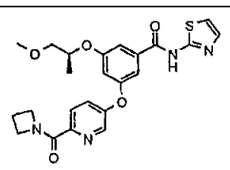
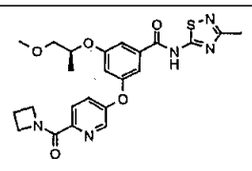
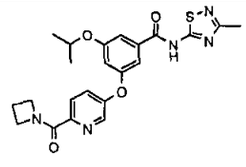
Example 3: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.2 g, 0.66 mmol), 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (158 mg, 0.66 mmol), cesium carbonate (640 mg, 1.97 mmol) and bromotris(triphenylphosphine)copper(I) (62 mg, 0.07 mmol) in DMA (5 mL) was stirred in a 'Biotage initiator Microwave' for 3 hours. The mixture was allowed to reach RT and pressure and was partitioned between ethyl acetate (50 mL) and water (50 mL). The ethyl acetate layer was separated, washed with water (5 x 50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the desired compound (113 mg). The compound was partially crystallised from methanol. The material was also partially crystallised from isopropyl alcohol / isohexane or ethyl acetate / isohexane. Mpt (melting onset) 132.7°C. ^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.36 (quin, 2H), 3.40 (s, 3H), 3.61 - 3.47 (m, 2H), 3.78 (s, 3H), 4.25 (t, 2H), 4.58 (sextet, 1H), 4.72 (t, 2H), 6.80 (t, 2H), 7.11 (s, 1H), 7.31 - 7.27 (m, 2H), 7.40 - 7.35 (m, 1H), 8.12 (d, 1H), 8.32 (s, 1H), 8.32 (s, 1H). *m/z* 466 $(M+H)^+$

The following compounds were synthesised in an analogous fashion from the appropriate phenol and bromopyridine:

Example	Structure	m/z	NMR
3a		466 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.40 (quintet, 2H), 3.41 (s, 3H), 3.49 - 3.62 (m, 2H), 3.80 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.60 (sextet, 1H), 6.80 (m, 2H), 7.10 (t, 1H), 7.27 (t, 1H), 7.30 (d, 1H), 7.62 (t, 1H), 8.51 (d, 1H), 8.61 (s, 2H)
3b		436 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.40 (quintet, 2H), 3.80 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.60 (septet, 1H), 6.74 (t, 1H), 6.80 (s, 1H), 7.07 (s, 1H), 7.07 (s, 1H), 7.30 (d, 1H), 7.62 (t, 1H), 8.51 (s, 1H), 8.61 (s, 2H)

3c		439 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 2.38 (quintet, 2H), 4.25 (t, 2H), 4.58 (septet, 1H), 4.73 (t, 2H), 6.80 (s, 1H), 6.98 (d, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.35 (m, 2H), 8.13 (d, 1H), 8.31 (d, 1H), 12.15 (s, 1H)
3d		436 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.26 (quintet, 2H), 3.69 (s, 3H), 4.18 (t, 2H), 4.49 (septet, 1H), 4.63 (t, 2H), 6.65 (s, 1H), 6.72 (s, 1H), 7.00 (s, 1H), 7.15 (m, 1H), 7.20 (m, 2H), 7.28 (m, 1H), 8.02 (d, 1H), 8.21 (d, 1H), 8.63 (s, 1H)
3e		469 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.33 (d, 6H), 2.36 (quintet, 2H), 3.38 (s, 3H), 3.48-3.60 (m, 2H), 4.25 (t, 2H), 4.59 (sextet, 1H), 4.72 (t, 2H), 6.88 (m, 1H), 6.97 (d, 1H), 7.19 (d, 1H), 7.28 (m, 2H), 7.38 (m, 2H), 8.12 (d, 1H), 8.30 (d, 1H), 12.30 (s, 1H)
3f		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.29 (quintet, 2H), 2.44 (s, 3H), 3.31 (s, 3H), 3.4 - 3.52 (m, 2H), 4.15 (m, 2H), 4.55 (sextet, 1H), 4.65 (t, 1H), 6.80 (m, 1H), 7.25 (m, 2H), 7.40 (m, 1H), 7.60 (m, 1H), 8.00 (d, 1H), 8.21 (s, 1H).
3g		454 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.30 (d, 6H), 2.29 (quintet, 2H), 2.44 (s, 3H), 4.18 (m, 2H), 4.55 (septet, 1H), 4.65 (t, 1H), 6.74 (m, 1H), 7.18 (m, 1H), 7.30 (m, 1 H), 7.40 (m, 1H), 8.00 (d, 1H), 8.23 (s, 1H), 10.05 (s, 1H)

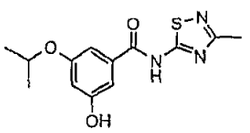
The preparation of the required bromopyridines is described earlier.

The preparation of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide, 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide, 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-1,3-thiazol-2-ylbenzamide, 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide and 3-

hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide is described earlier.

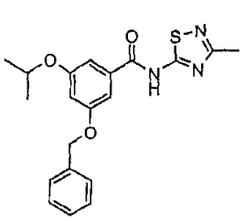
The preparation of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide used in **Example 3g** is described below:

3-Hydroxy-5-[(1-methylethyl)oxyl-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide



A solution of 3-[(1-methylethyl)oxy]-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)-5-[(phenylmethyl)oxy]benzamide (33 g, 86 mmol), trifluoroacetic acid (160 mL) and thioanisole (50.5 mL) was stirred at ambient temperature for 48 hours. The TFA was removed *in vacuo* and the residue poured into saturated sodium bicarbonate solution (300 mL) and extracted into ethyl acetate (twice). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was triturated with DCM and washed with 5% ethyl acetate in isohexane to give the desired compound (12.8 g). ^{1}H NMR δ (d_6-DMSO): 1.31 (d, 6H), 2.51 (s, 3H), 4.67 (sept, 1H), 6.58 (s, 1H), 7.08 (s, 1H), 7.24 (s, 1H), 9.88 (s, 1H), 13.25 (brs, 1H). *m/z* 294 $(M+H)^+$

3-[(1-Methylethyl)oxyl-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)-5-[(phenylmethyl)oxy]benzamide

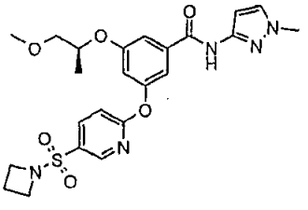


DMF (2 drops) was added to a solution of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (29.6 g, 0.103 mol) and oxalyl chloride (10.78 mL, 0.12 mol) in DCM (500 mL) The mixture was stirred at ambient temperature for 4 hours and the DCM and excess oxalyl chloride removed *in vacuo*. The residual acid chloride was dissolved in DCM (220 mL) and added dropwise to 5-amino-3-methyl-1,2,4-thiadiazole

(12.43 g, 0.108 mol) and triethylamine (30.34 mL, 0.216 mol) in DCM (220 mL), at 0°C. The reaction was allowed to warm and stirred at ambient temperature for 72 hours. The DCM was removed *in vacuo*, and the residue partitioned between ethyl acetate (400 mL) and 1N hydrochloric acid (200 mL). The ethyl acetate layer was washed sequentially with saturated aqueous sodium hydrogen carbonate (200 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 20% ethyl acetate in isohexane, to give the desired compound (33 g). ^{1}H NMR δ ($CDCl_3$): 1.32 (d, 6H), 2.31 (s, 3H), 4.51 (sept, 1H), 5.05 (s, 2H), 6.74 (m, 1H), 7.03 (m, 1H), 7.10 (m, 1H), 7.38 (m, 5H), 11.48 (brs, 1H). *m/z* 384 $(M+H)^+$

The preparation of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid is described above.

Example 4: 3-{[5-(Azetidin-1-ylsulfonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

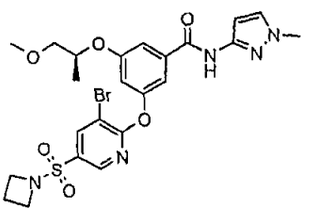


Triethylamine (0.025 mL, 0.18 mmol) then triethylsilane (0.96 mL, 6.03 mmol) were added to palladium (II) acetate (12 mg) in DCM (2 mL) and stirred under argon for 15 mins. 3-{[5-(Azetidin-1-ylsulfonyl)-3-bromopyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.175 g, 0.3 mmol) in DCM (2 mL) was added dropwise and the reaction stirred at RT for 24 hours. Methanol was added, the reaction filtered through celite and the solvent removed *in vacuo*. Ethyl acetate (30 mL) was added and the mixture washed with water (30 mL), citric acid (30 mL), brine (30 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give a white solid. This was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give the desired compound (69 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.09 (quin, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 3.69 (s, 3H), 3.76 (t, 4H), 4.52 (sextet, 1H), 6.73 (d, 1H), 6.87 (t, 1H), 7.02 (d, 1H), 7.17 (t, 1H), 7.20 (m, 1H), 7.28 (s, 1H), 8.04 (m, 1H), 8.54 (d, 1H), 8.65 (s, 1H). *m/z* 502 $(M+H)^+$

The preparation of 3-{[5-(azetidin-1-ylsulfonyl)-3-bromopyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

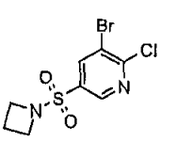
3-{[5-(Azetidin-1-ylsulfonyl)-3-bromopyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.2g, 0.66 mmol), 5-(azetidin-1-ylsulfonyl)-3-bromo-2-chloropyridine (204 mg, 0.66 mmol) and potassium carbonate (181 mg, 1.31 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and water, the organic layer washed with brine (50 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give a brown oil which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (175 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.12 (quin, 2H), 3.33 (s, 3H), 3.54 - 3.40 (m, 2H), 3.68 (s, 3H), 3.79 (t, 4H), 4.52 (sextet, 1H), 6.73 (d, 1H), 6.89 (t, 1H), 7.18 (t, 1H), 7.21 (d, 1H), 7.30 (t, 1H), 8.27 (d, 1H), 8.38 (d, 1H), 8.77 (s, 1H). *m/z* 580, 582 $(M+H)^+$

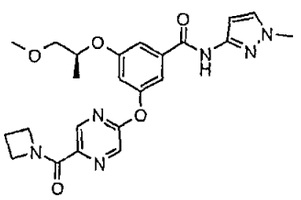
5-(Azetidin-1-ylsulfonyl)-3-bromo-2-chloropyridine



Azetidine hydrochloride (0.32 g, 3.44 mmol) was added to a solution of 3-bromo-2-chloropyridine-5-sulfonyl chloride (1 g, 3.44 mmol) in DCM (4 mL) and pyridine (10 mL) and stirred at RT for 22 hours. The solvent was removed *in vacuo* and ethyl acetate (30 mL) added. The organic phase was washed with 1M hydrochloric acid (20 mL), water (20 mL), brine (20 mL), dried (MgSO4), filtered and the solvent removed *in vacuo* to give the desired compound (0.4 g).

^{1}H NMR δ ($CDCl_3$): 2.18 (quin, 2H), 3.83 (t, 4H), 8.26 (s, 1H), 8.66 (s, 1H).

Example 5: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

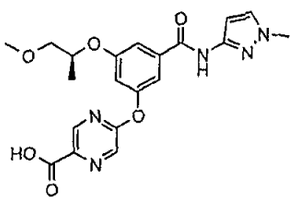


DIPEA (0.28 mL, 1.59 mmol) was added to a suspension of 5-[(3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (170 mg, 0.4 mmol), HATU (318 mg, 0.84 mmol) and azetidine hydrochloride (75 mg, 0.8 mmol) in DMF (5 mL) and the mixture stirred at RT for 72 hours. Ethyl acetate (40 mL) was added and washed with water (2 x 30 mL), brine (30 mL), dried (MgSO4), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane, to give the desired compound (48 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.31 (quin, 2H), 3.32 (s, 3H), 3.41 - 3.55 (m, 2H), 3.71 (s, 3H), 4.19 (t, 2H), 4.52 (m, 1H), 4.60 (t, 2H), 6.72 (s, 1H), 6.86 (m, 1H), 7.16 (m, 1H), 7.20 (m, 1H), 7.28 (m, 1H), 8.25 (s, 1H), 8.52 (s, 1H), 8.52 (s, 1H). *m/z* 467 $(M+H)^+$

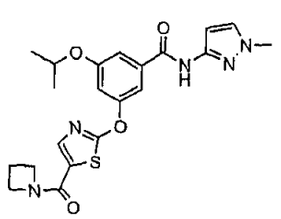
The preparation of 5-[(3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid is described below:

5-[(3-{[(1*S*)-1-Methyl-2-(methyloxy)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid



A mixture of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.226 g, 0.74 mmol), methyl 5-chloropyrazine-2-carboxylate (192 mg, 1.11 mmol) and potassium carbonate (205 mg, 1.48 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 4 hours. The solvent was removed *in vacuo* and water (30 mL) added. The mixture was acidified and extracted into ethyl acetate (3 x 50 mL), the combined organics washed with brine (30 mL), dried (MgSO4), filtered and reduced *in vacuo* to give a brown oil which was a mixture of the acid and methyl ester. Lithium hydroxide monohydrate (78 mg, 1.85 mmol) in water (2 mL) was added to the mixture of acid and ester (326 mg, 0.74 mmol) in THF (4 mL) and the mixture stirred at RT for 20 hours. The THF was removed *in vacuo* and the aqueous residue washed with ethyl acetate (20 mL) to remove impurities then acidified with 1M citric acid. The product was extracted into ethyl acetate (2 x 100 mL) and the combined organics washed with brine (50 mL), dried (MgSO4), filtered and reduced *in vacuo* to give a yellow solid (0.17 g). *m/z* 428 $(M+H)^+$

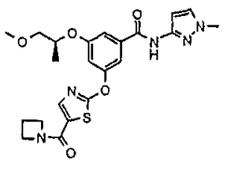
Example 6: 3-{[5-(Azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



Cesium carbonate (488 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (187 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazole (152 mg, 0.75 mmol) in acetonitrile (5 mL)

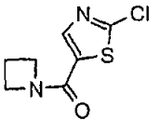
and the stirred mixture heated at 160^0 in a Biotage Initiator Microwave for 2 hours. The mixture was cooled to RT and pressure, poured onto water (75 mL) then extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica eluting with ethyl acetate, to give the desired compound (142 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.4 (m, 2H), 3.7 (s, 3H), 4.1 – 4.4 (m, 4H), 4.5 (m, 1H), 6.75 (s, 1H),6.9 (s, 1H), 7.2 (s, 1H), 7.25 (d, 1H), 7.4 (s, 1H) and 8.95 (s, 1H). *m/z* 442 $(M+H)^+$.

The following example was made in an analogous fashion from 5-(azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazole and 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide.

Example	Structure	m/z	NMR
6a		472 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.35 (m, 2H), 3.3 (s, 1H), 3.4-3.55 (m, 2H), 3.7 (s, 3H), 4.1 – 4.4 (m, 4H), 4.5 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.25 (s, 1H), 7.3 (d, 2H), 7.4 (s, 1H) and 8.9 (s, 1H).

The preparation of 5-(azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazole is described below:

5-(Azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazole

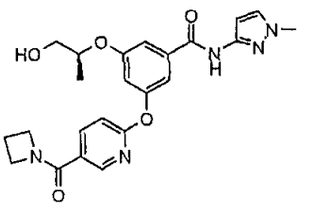


To a solution of 2-chlorothiazole-5-carboxylic acid (815 mg, 5 mmol) in dichloromethane (10 mL) was slowly added oxalyl chloride (0.53 mL, 6 mmol) and then N,N dimethylformamide (1 drop) with stirring. The mixture was stirred for 16 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (100ml). The crude material was dissolved in dichloromethane (10 mL) and slowly added to a stirred suspension of azetidine hydrochloride (560 mg, 6 mmol) and triethylamine (2.5 mL, 18 mmol) in dichloromethane (25 mL). The mixture was stirred at ambient

temperature for 2 hours before the organics were removed *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and water (25 mL), the organic layer washed with brine (25 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica with 40% ethyl acetate in *iso*-hexane as eluant to give 5-(azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazoline. ^{1}H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.1 – 4.4 (m, 4H), 4.55 (m, 1H), 7.2 (s, 1H) and 7.75 (s, 1H); m/z 203 $(M+H)^+$.

The preparation of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide are described earlier.

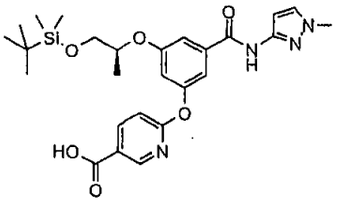
Example 7: 3-{[5-(Azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A solution of 6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylic acid (0.20 g, 0.378 mmol), azetidine hydrochloride (0.106 g, 0.114 mmol), HATU (0.302 g, 0.794 mmol) and DIPEA (0.39 mL, 0564 mmol) in DMF (7 mL) was stirred at RT overnight. 3.5M Hydrochloric acid (0.5 mL) was added and the solution left to stir for 20 minutes. The solution was neutralised with saturated sodium bicarbonate solution. Water (20 mL) was added and the solution extracted with ethyl acetate (50 mL). The ethyl acetate layer was washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired product (27 mg). ^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.38 (quintet, 2H), 3.77 (m, 2H), 3.80 (s, 3H), 4.29 (d, 4H), 4.57 (sextet, 1H), 6.81 (d, 1H), 6.91 (t, 1H), 6.99 (d, 1H), 7.27 (m, 2H), 7.38 (m, 1H), 8.42 (d, 1H), 8.86 (s, 1H). *m/z* 452 $(M+H)^+$

The preparation of 6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylic acid is described below:

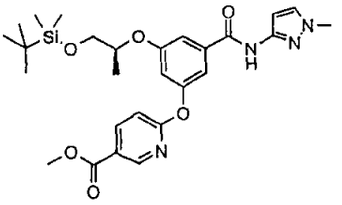
6-[(3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylic acid



A solution of lithium hydroxide monohydrate (0.10 g, 4.17 mmol) in water (15 mL) was added to a solution of methyl 6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylate (0.90 g, 1.67 mmol) in THF (30 mL). The mixture was allowed to stir at RT overnight. The THF was removed *in vaccuo* and the resulting solution was partitioned between water (50 mL) and ethyl acetate (75 mL), then the ethyl acetate layer separated, washed with brine and dried ($MgSO_4$). The aqueous layer was then taken to pH 7 by addition of 1N hydrochloric acid (5.2 mL) and extracted with ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$). The ethyl acetate layers were combined and evaporated to give the required product (0.84 g).

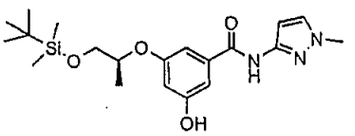
^{1}H NMR δ ($CDCl_3$): 0.05 (d, 6H), 0.88 (s, 9H), 1.36 (d, 3H), 3.70-3.88 (m, 5H), 4.52-4.61 (sex, 1H), 6.98 (d, 2H), 7.01 (d, 1H), 6.28 (s, 1H), 7.44 (s, 1H), 7.57 (s, 1H), 8.04 (m, 1H), 8.72 (s, 1H), 10.62 (s, 1H). *m/z* 527 $(M+H)^+$

Methyl 6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylate



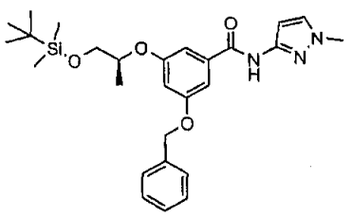
A solution of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1.00 g, 2.47 mmol), methyl 6-chloronicotinate (0.450 g, 2.60 mmol), and cesium carbonate (1.204 g, 3.71 mmol) in acetonitrile (15 mL) was heated at 160°C using microwave heating for 90 minutes. The acetonitrile was removed *in vaccuo* and the residual oil partitioned between water (50 mL) and ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired compound (0.977 g).
^{1}H NMR δ ($CDCl_3$): 0.05 (d, 6H), 0.87 (s, 9H), 1.34 (d, 3H), 3.54 (m, 3H), 3.79 (s, 3H), 3.93 (s, 3H), 4.59 (sextet, 1H), 6.79 (d, 1H), 6.92 (t, 1H), 6.96 (s, 1H), 6.99 (s, 1H), 7.20 (t, 1H), 7.27 (d, 1H), 7.33 (t, 1H), 8.28 (d, 1H), 8.31 (d, 1H), 8.39 (s, 1H), 8.82 (d, 1H). *m/z* $(M+H)^+$ 541

3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



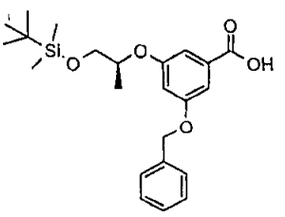
3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1.8 g, 3.64 mmol) was dissolved in methanol (50 mL) and the flask evacuated and purged with nitrogen (3 times). 10% Palladium on carbon (0.2 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at ambient temperature for 16 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off, and the filtrate concentrated *in vacuo* to give the desired compound (1.45 g). ^{1}H NMR δ (d_6-DMSO): 0.02 (d, 6H), 0.83 (s, 9H), 1.18 (d, 3H), 3.66 (m, 2H), 3.72 (s, 3H), 4.51 (m, 1H), 6.42 (m, 1H), 6.52 (m, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.55 (m, 1H), 9.58 (br s, 1H), 10.59 (br s, 1H). *m/z* 406 $(M+H)^+$

3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



DIPEA (4.06 g, 23.4 mmol) was added to a suspension of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (2.43 g, 5.84 mmol), 3-amino-1-methylpyrazole (0.85 g, 8.76 mmol) and HATU (4.66 g, 12.3 mmol) in DMF (50 mL) and stirred at ambient temperature for 16 hours. The resultant mixture was partially reduced *in vacuo*, poured onto water (100 mL) and extracted with diethyl ether (2 x 50 mL). The extracts were washed with water and brine then dried ($MgSO_4$), filtered and reduced to an opaque gum which partially crystallized. The crude product was purified by column chromatography, eluting with 0-100% ethyl acetate in isohexane, to give the title compound as a colourless oil (1.87g).
^{1}H NMR δ (d_6-DMSO): 0.02 (d, 6H), 0.84 (s, 9H), 1.21 (d, 3H), 3.68 (d, 2H), 3.76 (s, 3H), 4.58 (m, 1H), 5.13 (s, 2H), 6.56 (m, 1H), 6.70 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.29-7.46 (m, 5H), 7.57 (m, 1H), 10.74 (br s, 1H). *m/z* 496 $(M+H)^+$

3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid

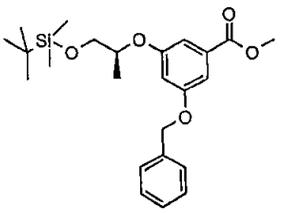


Methyl 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoate (3.0 g, 6.98 mmol) was dissolved in THF (50 mL) and water (10mL) and lithium hydroxide monohydrate (586 mg, 13.95 mmol) added. The resultant mixture was heated with stirring at 45°C for 2 hours, then at ambient temperature for 16

hours, and at 45°C for a further 4 hours. Water (40 mL) was added and the solvent removed *in vacuo*. The resultant solution was acidified carefully with 1M citric acid (2 equivalents), washed with water and brine then dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the title compound as a colourless gum (2.58 g).

^{1}H NMR δ (d_6-DMSO): 0.02 (d, 6H), 0.84 (s, 9H), 1.17 (d, 3H), 3.66 (m, 2H), 4.43 (m, 1H), 5.05 (s, 2H), 6.56 (br s, 1H), 7.10 (br s, 1H), 7.17 (br s, 1H), 7.25-7.44 (m, 5H), 7.60 (br s, 1H).

Methyl 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoate

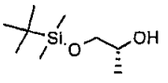


(2*R*)-1-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}propan-2-ol (3.31 g, 17.4 mmol) was added to a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (3.00 g, 11.6 mmol) in THF (50 mL) at 0°C followed by addition of triphenylphosphine (4.57 g, 17.4 mmol) then DIAD (3.43 mL, 17.4 mmol) and the reaction was warmed to RT and stirred for 16 h. The reaction was quenched with water (100 mL) and diethyl ether (400 mL) and the organic layer was separated then dried ($MgSO_4$) and evaporated. Purification by column chromatography, eluting with 1:15 to 1:5 ethyl acetate:hexane, afforded the title compound as a colourless oil (4.00 g, 80%).

^{1}H NMR δ ($CDCl_3$): 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.29 (d, 3H), 3.63 (dd, 1H), 3.78 (dd, 1H), 3.92 (s, 3H), 4.44 (m, 1H), 5.08 (s, 2H), 6.77 (m, 1H), 7.40 (m, 7H).

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

(2*R*)-1-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}propan-2-ol

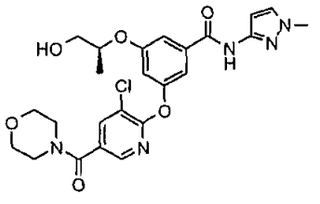


tert-Butyl(dimethyl)silyl chloride (5.90 g, 39.5 mmol) was added to a solution of (2*R*)-propane-1,2-diol (3.00 g, 39.5 mmol) in DCM (100 mL) followed by diisopropylethylamine (7.10 g, 55.3 mmol) and the reaction was stirred under argon for 72 h. The reaction was diluted with diethyl ether (500 mL) and water (140 mL) and the organic layer was separated then dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography, eluting with 1:15 to 1:10 ethyl acetate: hexane, afforded the title compound as a colourless oil (6.00 g, 80%).

^{1}H NMR δ ($CDCl_3$): 0.10 (m, 6H), 0.92 (s, 9H), 1.14 (d, 3H), 2.42 (d, 1H), 3.38 (dd, 1H), 3.60 (dd, 1H), 3.82 (m, 1H).

The data matched that reported in the literature (*J. Org. Chem.*, **1998**, *53*, 2300).

Example 8: 3-{[3-Chloro-5-(morpholin-4-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

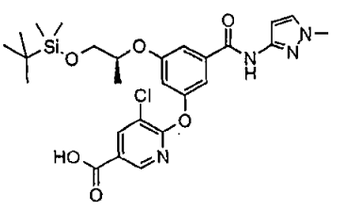


A solution 5-chloro-6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylic acid (0.15 g, 0.267 mmol), morpholine (0.07 mL, 0.803 mmol), HATU (0.213 g, 0.560 mmol) and DIPEA (0.15 mL, 0.861 mmol) in DMF (7 mL) was stirred at RT for 2 days. Water (20 mL) was added and the solution extracted with ethyl acetate (50 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 1% methanol in ethyl acetate. 3.5M Hydrochloric acid (0.5 mL) was added to a solution of the residual solid taken up in methanol (5 mL) and allowed to stir at RT for 20 minutes. The solution was neutralised with saturated sodium bicarbonate solution and the methanol removed *in vaccuo* and the residual solution partitioned between water (20 mL) and ethyl acetate. The ethyl acetate

layer was separated and washed with brine, dried ($MgSO_4$) and evaporated to give the desired product (34 mg). ^{1}H NMR δ (d6-DMSO): 1.28 (d, 3H), 3.58 (m, 10H), 3.81 (s, 3H), 4.61 (sextet, 1H), 4.89 (t, 1H), 6.60 (d, 1H), 7.03 (t, 1H), 7.41 (s, 1H), 7.54 (s, 1H), 7.63 (d, 1H), 8.20 (q, 2H), 10.84 (s, 1H). *m/z* 516 $(M+H)^+$

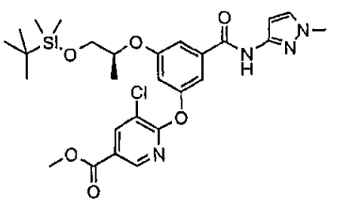
The preparation of 5-chloro-6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylic acid is described below:

5-Chloro-6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxyl-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylic acid



To a solution of methyl 5-chloro-6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylate (1.2 g, 2.09 mmol) in THF (50 mL) was added a solution of lithium hydroxide monohydrate (0.219 g, 5.22 mmol) in water (30 mL). The mixture was allowed to stir under RT overnight. The THF was removed *in vaccuo* and the resulting solution was partitioned between water (50 mL) and ethyl acetate (75 mL), and the ethyl acetate layer separated, washed with brine and dried ($MgSO_4$). The aqueous layer was then adjusted to pH 7 by addition of 1N hydrochloric acid (5.2 mL) and partitioned between ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$). The ethyl acetate layers were combined and evaporated to give the required product (1.1 g). ^{1}H NMR δ (d_6-DMSO): 0.01 (d, 6H), 0.82 (s, 9H), 1.22 (d, 3H), 3.73 (m, 2H), 3.76 (s, 3H), 4.55 (sextet, 1H), 6.55 (d, 1H), 6.90 (t, 1H), 7.30 (s, 1H), 7.44 (s, 1H), 7.58 (d, 1H), 8.36 (d, 1H), 8.19 (d, 1H), 8.51 (s, 1H). *m/z* $(M+H)^+$ 562

Methyl 5-chloro-6-[(3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyridine-3-carboxylate

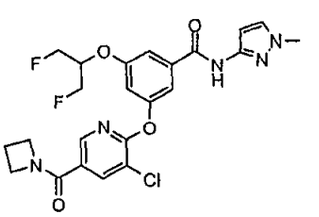


A solution of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1.0 g, 2.47 mmol), ethyl 5,6-dichloronicotinate (0.57 g, 2.59 mmol), and potassium carbonate (0.855 g, 6.14 mmol) in acetonitrile (15 mL) was heated at 160°C for 4 hours using microwave heating. The acetonitrile was removed *in vaccuo* and the residual oil partitioned between water (50 mL) and ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in hexane to give the desired compound (1.1 g). The analytical data indicated that transesterification had occurred at some stage in the procedure to furnish the methyl ester.

^{1}H NMR δ ($CDCl_3$): 0.05 (d, 6H), 0.87 (s, 9H), 1.30 (d, 3H), 3.72 (s, 3H), 3.73 (m, 1H), 3.93 (s, 3H), 4.47 (sextet, 1H), 6.80 (d, 1H), 6.93 (t, 1H), 7.19 (t, 1H), 7.25 (d, 1H), 7.26 (s, 1H), 7.34 (t, 1H), 8.35 (d, 1H), 8.61 (d, 1H), 8.97 (s, 1H); *m/z* $(M+H)^+$ 575

The preparation of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described earlier.

Example 9: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



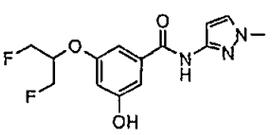
A mixture of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (200 mg, 0.64 mmol), 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (164 mg, 0.71 mmol) and potassium carbonate (178 mg, 1.28 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave'at 120°C for 4 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water (100 mL), the organic layer washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (237 mg).

^{1}H NMR δ ($CDCl_3$): 2.39 (quintet, 2H), 3.74 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.63 (m, 2H), 4.74 (m, 3H), 6.81 (s, 1H), 7.01 (s, 1H), 7.29 (m, 1H), 7.31 (s, 1H), 7.42 (s, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 9.26 (s, 1H). *m/z* 506 $(M+H)^+$

The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine is described above.

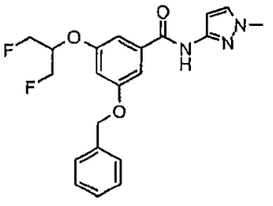
The preparation of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A solution of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (2.46 g, 6.13 mmol) and 10% by weight palladium on carbon (0.246 g) in ethanol (100 mL) was allowed to stir at RT, under a hydrogen atmosphere overnight. The solution was filtered through Celite ® and the cake washed with methanol (100 mL). The solution was evaporated to give the desired compound (1.78 g). ^{1}H NMR δ (d_6-DMSO): 3.78 (s, 3H), 4.72 (m, 4H), 4.97 (m, 1H), 6.57 (d, 2H), 7.03 (s, 1H), 7.16 (s, 1H), 7.59 (s, 1H). *m/z* 312 $(M+H)^+$

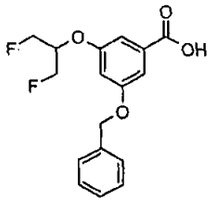
3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



A solution 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (3.00 g, 9.31 mmol), 3-amino-1-methylpyrazole (1.83 g, 18.6 mmol), HATU (4.60 g, 12.1 mmol) and DIPEA (3.25 mL, 18.6 mmol) in DMF (12 mL) was stirred at RT overnight. Water (150 mL) was added and the solution partitioned with ethyl acetate (250 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired product (2.46 g).

^{1}H NMR δ ($CDCl_3$): 3.69 (s, 3H), 4.57 (m, 5H), 5.00 (s, 2H), 6.70 (t, 1H), 6.74 (d, 1H), 7.01 (t, 1H), 7.08 (t, 1H), 7.21 (d, 1H), 7.30 (m, 5H), 8.68 (s, 1H); *m/z* 402 $(M+H)^+$

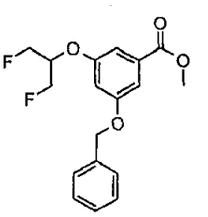
3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid



A solution of lithium hydroxide monohydrate (2.32 g, 55.1 mmol) in water (100 mL) was added to a solution of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate (7.41 g, 22.0 mmol) in THF (200 mL) and the mixture allowed to stir at RT overnight. The THF was removed *in vacuo* and the resulting solution partitioned between water (100 mL) and ethyl acetate (250 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$). The aqueous layer was then adjusted to pH 7 by addition of 1M hydrochloric acid and extracted with ethyl acetate (75 mL). The ethyl acetate layer was separated, washed with brine and dried ($MgSO_4$). The ethyl acetate layers were combined and evaporated to give the required product (6.404 g).

^{1}H NMR δ (d_6-DMSO): 4.74 (m, 4H), 5.08 (s, 2H), 6.67 (s, 1H), 6.67 (s, 1H), 7.23 (s, 1H), 7.37 (m, 5H). *m/z* 231 $(M-H)^-$

Methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate

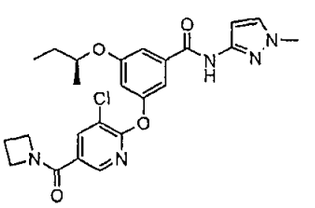


DIAD (7.63 mL, 38.7 mmol) was added in a dropwise fashion to a solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (5.00 g, 19.4 mmol), 1,3-difluoropropan-2-ol (3 mL, 38.7 mmol), and triphenylphosphine (10.16 g, 38.7 mmol) in THF (100 mL) under an inert atmosphere at 0°C. The solution was allowed to reach RT and left to stir for 2 days. The THF was removed *in vacuo* and the residual oil slurried with a mixture of 20% ethyl acetate in isohexane. After allowing to stir for 90 minutes the mixture was filtered and the filtrate evaporated. The residual was oil chromatographed on silica, eluting with 30% ethyl acetate in isohexane, to give the desired compound (7.41g).

^{1}H NMR δ (d_6-DMSO): 3.85 (s, 3H), 4.71 (m, 4H), 5.03 (m, 1H), 5.17 (s, 2H), 7.01 (t, 1H), 7.20 (m, 2H), 7.40 (m, 5H). *m/z* 335 $(M-H)^-$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate is described above.

Example 10: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A solution of 3-hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (116 mg, 0.4 mmol) and the 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (111 mg, 0.48 mmol) in acetonitrile (2 mL) containing potassium carbonate (111 mg, 0.8

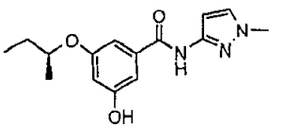
mmol) was heated with stirring in the microwave reactor for 6 hours at 160°C. The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure and purified by chromatography on silica, eluting with 50-100% ethyl acetate in hexane, to give the required product (177 mg).

^{1}H NMR δ ($CDCl_3$): 0.91 (t, 3H), 1.25 (d, 3H), 1.52 - 1.75 (m, 2H), 2.32 (quin, 2H), 3.72 (s, 3H), 4.17 (t, 2H), 4.25 - 4.34 (m, 3H), 6.73 (d, 1H), 6.81 (t, 1H), 7.12 (s, 1H), 7.21 (d, 1H), 7.24 (s, 1H), 8.09 (d, 1H), 8.18 (d, 1H), 8.54 (s, 1H); *m/z* 484 $(M+H)^+$

The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine was described earlier.

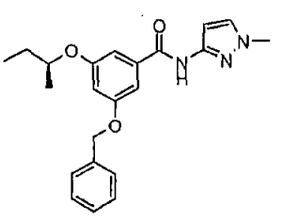
The preparartion of 3-hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

3-Hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



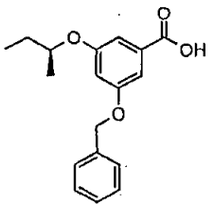
A solution of 3-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (900 mg) in THF (5 mL) and ethanol (5 mL) containing 10% palladium on carbon was stirred under an atmosphere of hydrogen overnight. The palladium on carbon was removed by filtration and the filtrate evaporated under reduced pressure to give the required compound as a white solid (683 mg). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.27 (d, 3H), 1.54 - 1.80 (m, 2H), 3.79 (s, 3H), 4.31 (q, 1H), 6.57 (t, 1H), 6.81 (d, 1H), 6.96 (s, 1H), 6.98 (s, 1H), 7.30 (s, 1H), 7.57 (s, 1H), 8.84 (s, 1H); *m/z* 290$(M+H)^+$

3-{[(1*S*)-1-Methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



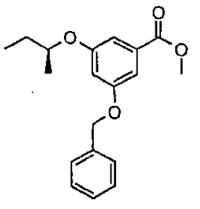
HATU (1.19 g, 3.13 mmol) was added to 3-{[(1*S*)-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (750 mg, 2.5 mmol) and 3-amino-1 methyl pyrazole (291 mg, 3 mmol) in DMF (5 mL) followed by addition of DIPEA (0.807 mL, 6.25 mmol) and the reaction was stirred for 16 hours. The reaction mixture was added to ethyl acetate (30 mL), washed with water (10 mL), 2N citric acid (10 mL), saturated aqueous sodium hydrogencarbonate (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and evaporated to a gummy residue. The residue was taken up in 50% ether in ethylacetate (50 mL), washed with 2N hydrochloric acid (10 mL), water (10 mL), saturated aqueous sodium hydrogencarbonate (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and evaporated to a foam (900 mg) which was used without further purification in the next step. ^{1}H NMR δ ($CDCl_3$): 0.96 (t, 3H), 1.28 (d, 3H), 1.51-1.80 (m, 2H), 3.78 (s, 1H), 4.31 (q, 1H), 5.06 (s, 2H), 6.68 (t, 1H), 6.82 (d, 1H), 7.00 (s, 1H), 7.06 (s, 1H), 7.29 (s, 3H), 7.31 - 7.47 (m, 5H), 8.63 (s, 1H); *m/z* 380 $(M+H)^+$

3-{[(1*S*)-1-Methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid



Methyl 3-{[(1*S*)-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate (14.87 g, 47.36 mmol) was vigorously stirred in a mixture of aqueous 1M sodium hydroxide (120 mL) and THF at approximately 45°C for 4 hours. The bulk of the THF was removed under reduced pressure and the resultant solution partitioned between water and diethyl ether. The aqueous phase was acidified with 2M hydrochloric acid and then extracted with ethyl acetate. The organics were dried ($MgSO_4$) and concentrated *in vacuo* gave a white solid (11.5 g). ^{1}H NMR δ ($CDCl_3$): 0.90 (t, 3H), 1.20 (d, 3H), 1.49 - 1.69 (m, 2H), 4.33 - 4.46 (m, 1H), 5.12 (s, 2H), 6.75 - 6.79 (m, 1H), 6.99 - 7.03 (m, 1H), 7.06 - 7.11 (m, 1H), 7.26 - 7.47 (m, 5H)

Methyl 3-{[(1*S*)-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate

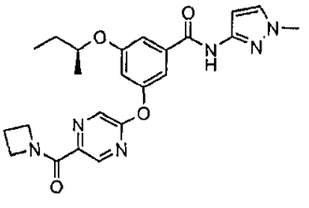


A solution of DIAD (16.6 mL, 84.0 mmol) in dry THF (100 mL) was added dropwise to a cooled (ice bath) stirred mixture of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (14.5 g, 56.2 mmol); R-(-)-sec-butanol (5 g, 67.0 mmol) and solid-supported triphenylphosphine (28 g, of 3 mmol per g loading, 84.0 mmol) in dry THF (400 mL) whilst maintaining the temperature below 10°C. The mixture was allowed to stir for 3 hours, then diluted with diethyl ether (800 mL) and filtered. Removal of the solvent gave a pale coloured oil, which was purified by column chromatography on silica, eluting with 25% ethyl acetate in hexane; to give the desired product (14.87 g).

^{1}H NMR δ ($CDCl_3$): 0.99 (t, 3H), 1.28 (d, 3H), 1.53 - 1.80 (m, 2H), 3.89 (s, 3H), 4.25 - 4.42 (m, 1H), 5.07 (s, 2H), 6.68 - 6.81 (m, 1H), 7.17 - 7.53 (m, 7H); *m/z* 313 $(M-H)^-$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

Example 11: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

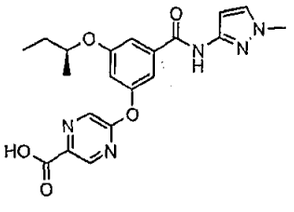


HATU (34 mg, 0.89 mmol) was added to 5-[(3-{[(1*S*)-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (190 mg, 0.4 mmol) and azetidine hydrochloride (84 mg, 0.89 mmol) in DMF (5 mL). DIPEA (0.311 mL, 1.79 mmol) was added and the reaction was stirred for 16 hours. The reaction mixture was added to ethyl acetate (20 mL), washed with water (10 mL), 2N citric acid (10

mL), saturated aqueous sodium hydrogencarbonate (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure to a gummy residue. The residue was purified by chromatography on silica, eluting with 50-100% ethyl acetate in hexane, to give a gum which was taken up in 50% ethyl acetate in ether and washed twice with water, brine (10 mL) then dried ($MgSO_4$) to give the desired product as a foam (58 mg).
^{1}H NMR δ ($CDCl_3$): 0.91 (t, 3H), 1.25 (d, 3H), 1.51 - 1.75 (m, 2H), 2.31 (quin, 2H), 3.72 (s, 3H), 4.19 (t, 2H), 4.29 (q, 1H), 4.62 (t, 2H), 6.73 (d, 1H), 6.80 (t, 1H), 7.13 (t, 1H), 7.21 (d, 1H), 7.23 (t, 1H), 8.26 (s, 1H), 8.52 (s, 1H), 8.79 (s, 1H); *m/z* 451 $(M+H)^+$

The preparation of 5-[(3-{[(1*S*)-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid is described below:

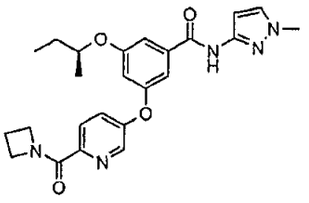
5-[(3-{[(1*S*)-1-Methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid



A solution of 3-hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (116 mg, 0.4 mmol) and the methyl 5-chloropyrazine-2-carboxylate (83 mg, 0.48 mmol) in acetonitrile (2 mL) containing potassium carbonate (111 mg, 0.8 mmol) was heated with stirring in the microwave for 6 hours at 160°C. Analytical LC-MS showed formation of the acid but no ester. The reaction mixture was dissolved in water (10 mL), acidified with 2N citric acid and extracted with ethyl acetate (5 x 20 mL), washed with brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to deliver the desired product (190 mg) which was used without purification in the next step.
m/z 412 $(M+H)^+$

The preparation of 3-hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier.

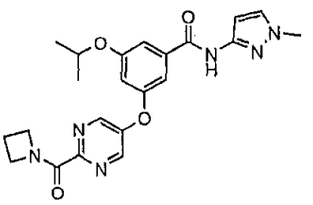
Example 12: 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of of 3-hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (0.116 g, 0.4 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (116 mg, 0.48 mmol), cesium carbonate (392 mg, 1.2 mmol) and bromotris(triphenylphosphine)copper(I) (38 mg, 0.04 mmol) in DMA (5 mL) was stirred in the microwave reactor at 160°C for 4 hours. The product was dissolved in ethyl acetate (20 mL) and water (15 mL) and the layers separated. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil which was chromatographed on silica, eluting with a gradient of 0-5% methanol in ethyl acetate, and then re-columned on silica, eluting with a gradient of 0-5% methanol in DCM, to give the desired compound as a white foam which crystallised on standing. The material was triturated with 50% ethyl acetate in hexane to give the required product as a white solid (95 mg). ^{1}H NMR δ ($CDCl_3$): 0.90 (t, 3H), 1.23 (d, 3H), 1.51 - 1.72 (m, 2H), 2.28 (quin, 2H), 3.73 (s, 3H), 4.18 (t, 2H), 4.28 (q, 1H), 4.64 (t, 2H), 6.67 (t, 1H), 6.72 (d, 1H), 6.99 (s, 1H), 7.15 (s, 1H), 7.22 (d, 1H), 7.31 (d, 1H), 8.04 (d, 1H), 8.26 (s, 1H), 8.41 (s, 1H); *m/z* 450 $(M+H)^+$

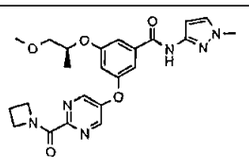
The preparation of 3-hydroxy-5-{[(1*S*)-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine were described earlier.

Example 13: 3-{[2-(Azetidin-1-ylcarbonyl)pyrimidin-5-yl]oxy}-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (250 mg, 0.91 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyrimidine (242 mg, 1.0 mmol), cesium carbonate (886 mg, 2.72 mmol) and bromotris(triphenylphosphine)copper(I) (423 mg, 0.45 mmol) in DMA (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 4 hours. The mixture was added to ethyl acetate (50 mL) and water (50 mL), the organic layer washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The residue was chromatographed on silica, eluting with a gradient of 0-10% methanol in ethyl acetate, to give the desired compound (199 mg). ^{1}H NMR δ ($CDCl_3$): 1.39 (d, 6H), 2.40 (quin, 2H), 3.82 (s, 3H), 4.35 (t, 2H), 4.62 (mult, 1H), 4.68 (t, 2H), 6.79 (s, 1H), 6.84 (s, 1H), 7.20 (s, 1H), 7.33 (mult, 2H), 8.60 (s, 2H), 8.97 (s, 1H); *m/z* 437 $(M+H)^+$

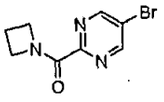
The following compound was synthesised in an analogous fashion from 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide.

Example	Structure	m/z	NMR
13a		467 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.37 (quin, 2H), 3.41 (s, 3H), 3.48 - 3.60 (m, 2H), 3.78 (s, 3H), 4.30 (t, 2H), 4.58 (mult, 1H), 4.64 (t, 2H), 6.80 (d, 1H), 6.83 (t, 1H), 7.19 (s, 1H), 7.30 (d, 1H), 7.33 (s, 1H), 8.55 (s, 2H), 8.93 (s, 1H)

The preparation of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide were described earlier.

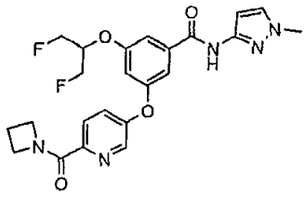
The preparation of 2-(azetidin-1-ylcarbonyl)-5-bromopyrimidine is described below:

2-(Azetidin-1-ylcarbonyl)-5-bromopyrimidine



Oxalyl chloride (1.50 mL, 16.8 mmol) then DMF (2 drops) were added to a mixture of 5-bromopyrimidine-2-carboxylic acid (prepared according to literature procedure described in WO 2005/028452) (2.86 g, 14.0 mmol) in DCM (40 mL). The reaction mixture was stirred at RT for 2 hours, the volatiles removed *in vacuo* and the residue dissolved in DCM (40 mL). Azetidine hydrochloride (1.44 g, 15.4 mmol) followed by triethylamine (4.29 mL, 30.8 mmol) were added and the mixture stirred at RT for 72 hours. The mixture was concentrated *in vacuo* and ethyl acetate (100 mL) added to the residue. The organics were washed with water (100 mL), citric acid solution (50 mL), saturated sodium bicarbonate solution (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow solid which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (0.86 g). ^1H NMR δ ($CDCl_3$): 2.39 (quin, 2H), 4.32 (t, 2H), 4.63 (t, 2H), 8.92 (s, 2H); *m/z* 242, 244 $(M+H)^+$

Example 14: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



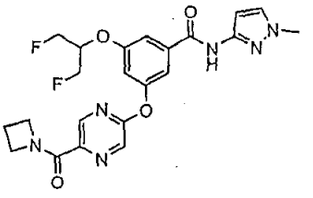
A mixture 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (100 mg, 0.32 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (86 mg, 0.35 mmol), cesium carbonate (209 mg, 0.64 mmol) and bromotris(triphenylphosphine)copper(I) (150 mg, 0.16 mmol) in DMA (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 3 hours. The reaction mixture was added to ethyl acetate (50 mL) and water (50 mL), the organic layer washed with brine (50 mL),

dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The residue was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane, to give a colorless oil which appeared to be a mixture of product and eliminated product (3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[1-(fluoromethyl)ethenyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide). This mixture was dissolved in chloroform (5 mL), TFA (0.5 mL) added and the mixture stirred for 2 hours. Complete degradation of eliminated product was observed by LCMS and the mixture concentrated *in vacuo* then water added. The mixture was neutralised and extracted into ethyl acetate (2 x 30 mL), washed with brine (30 mL), dried ($MgSO_4$), filtered and reduced to give a yellow oil which was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane, to give the desired compound (13 mg).

^{1}H NMR δ ($CDCl_3$): 2.29 (quin, 2H), 3.76 (s, 3H), 4.19 (t, 2H), 4.55 (mult, 2H), 4.67 (mult, 5H), 6.72 (s, 1H), 6.80 (mult, 1H), 7.09 (s, 1H), 7.25 (mult, 2H), 7.32 (mult, 1H), 8.06 (d, 1H), 8.26 (d, 1H), 8.43 (s, 1H); *m/z* 472 $(M+H)^+$

The preparation of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine were described earlier.

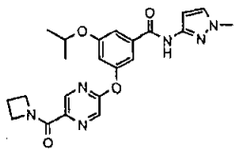
Example 15: 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



DIPEA (0.45 mL, 2.58 mmol) was added to a mixture of 5-[(3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (0.28 g, 0.65 mmol), azetidine hydrochloride (121 mg, 1.29 mmol) and HATU (516 mg, 1.36 mmol) in DMF (5 mL) and stirred at RT for 72 hours. Ethyl acetate (40 mL) was added and the organics washed with water (2 x 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give a

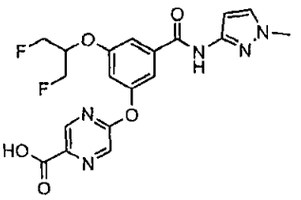
yellow oil which was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane, to give the desired compound (109 mg). ^{1}H NMR δ ($CDCl_3$): 2.32 (quin, 2H), 3.70 (s, 3H), 4.19 (t, 2H), 4.54 - 4.72 (m, 7H), 6.73 (s, 1H), 6.93 (t, 1H), 7.22 (d, 1H), 7.25 (s, 1H), 7.34 (s, 1H), 8.28 (d, 1H), 8.78 (d, 1H), 8.80 (s, 1H); *m/z* 473 $(M+H)^+$

The following compound was synthesised in an analogous fashion from 5-[(3-[(1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid.

Example	Structure	m/z	NMR
15a		437 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.38 (d, 6H), 2.40 (quin, 2H), 3.83 (s, 3H), 4.28 (t, 2H), 4.62 (sept, 1H), 4.71 (t, 2H), 6.82 (s, 1H), 6.89 (t, 1H), 7.23 (s, 1H), 7.31 (m, 2H), 8.35 (s, 1H), 8.55 (s, 1H), 8.88 (s, 1H)

The preparation of 5-[(3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid is described below:

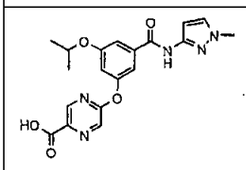
5-[(3-{[2-Fluoro-1-(fluoromethyl)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid



Lithium hydroxide monohydrate (77 mg, 1.82 mmol) in water (2 mL) was added to methyl 5-[(3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate (325 mg, 0.73 mmol) in THF (4 mL) and the mixture stirred at RT for 20 hours. The THF was removed *in vacuo* and the aqueous residue washed with ethyl acetate to remove impurities then acidified with 1M citric acid. Ethyl acetate was added and a white solid removed by filtration and dried *in*

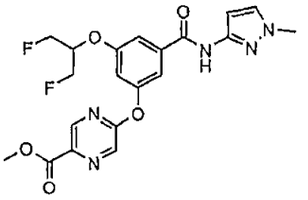
vacuo to give the desired compound as a white solid (0.28 g). ^{1}H NMR δ (d_6-DMSO): 3.79 (s, 3H), 4.77 (m, 4H), 5.12 (t, 1H), 6.59 (s, 1H), 7.22 (s, 1H), 7.50 (s, 1H), 7.62 (s, 2H), 8.69 (s, 1H), 8.80 (s, 1H), 10.90 (s, 1H), 13.50 (s, 1H), *m/z* 434 $(M+H)^+$

5-[(3-[(1-Methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid, used in the preparation of **Example 15a**, was prepared in an analogous fashion from methyl 5-[(3-[(1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate.

Structure	m/z	NMR
	398 $(M+H)^+$	

The preparation of methyl 5-[(3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate is described below:

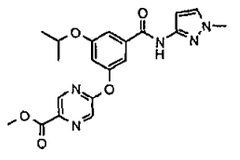
Methyl 5-[(3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate



A mixture of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (250 mg, 0.8 mmol), methyl 5-chloropyrazine-2-carboxylate (208 mg, 1.20 mmol) and potassium carbonate (222 mg, 1.61 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 120°C for 3 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (50 mL) and water (50 mL), the organic layer washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in*

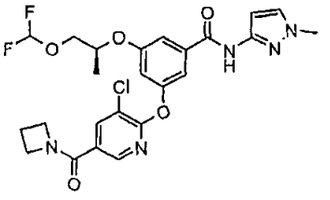
vacuo to give a yellow oil which was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane, to give the desired compound (0.325 g). ^{1}H NMR δ ($CDCl_3$): 3.71 (s, 3H), 3.96 (s, 3H), 4.56 (m, 2H), 4.68 (m, 3H), 6.73 (s, 1H), 6.95 (s, 1H), 7.22 (s, 1H), 7.27 (s, 1H), 7.36 (s, 1H), 8.46 (s, 1H), 8.67 (s, 1H), 8.67 (s, 1H); *m/z* 448 $(M+H)^+$

Methyl 5-[(3-[(1-methylethyl)oxy]-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate, used in **Example 15a**, was prepared in an analogous fashion from 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide.

Structure	m/z	NMR
	412(M+H)+	

The preparation of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide were described previously.

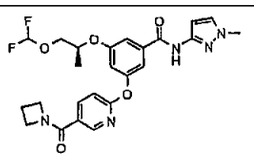
Example 16: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



A mixture of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (110 mg, 0.32 mmol), 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (75 mg, 0.32 mmol) and potassium carbonate (89 mg, 0.64 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue which was

washed with water (20 mL), brine (50mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The residue was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (92 mg). ^{1}H NMR δ ($CDCl_3$): 1.40 (d, 3H),,2.41 (quin, 2H), 3.81 (s, 3H), 4.01 (mult, 2H), 4.26 (t, 2H), 4.38 (t, 2H), 4.67 (sextet, 1H), 6.29 (t, 1H), 6.82 (d, 1H), 6.96 (t, 1H), 7.27 (t, 1H), 7.31 (d, 1H), 7.38 (t, 1H), 8.18 (d, 1H), 8.26 (d, 1H), 8.77 (s, 1H), *m/z* 536 $(M+H)^+$

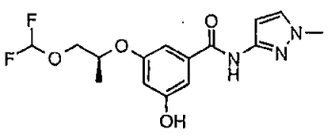
The following compound was made in an analogous fashion from 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine.

Example	Structure	m/z	NMR
16a		502 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 3H), 2.38 (quin, 2H), 3.73 (s, 3H), 3.98 (m, 2H), 4.25 (t, 2H), 4.36 (t, 2H), 4.62 (sextet, 1H), 6.27 (t, 1H), 6.81 (d, 1H), 6.90 (t, 1H), 7.00 (d, 1H), 7.24 (t, 1H), 7.27 (m, 1H), 7.33 (m, 1H), 8.08 (m, 1H), 8.42 (d, 1H), 9.12 (s, 1H)

The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine were described earlier.

The preparation of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

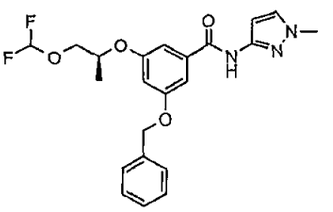
3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (0.1 g, 0.23 mmol) was dissolved in ethanol (3 mL) and

THF (3 mL) and the flask evacuated and purged with argon (3 times). 10% Palladium on carbon (0.01 g) was added and the flask further evacuated and finally purged with hydrogen gas. The reaction mixture was stirred at RT for 20 hours until completion. The reaction mixture was evacuated and purged with nitrogen (3 times). The catalyst was filtered off through celite and the filtrate concentrated *in vacuo* to give the desired compound (70 mg). ^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 3.71 (s, 3H), 3.80-3.95 (m, 2H), 4.51 (sextet, 1H), 5.96-6.36 (t, 1H), 6.53 (s, 1H), 6.73 (s, 1H), 6.91 (s, 1H), 6.96 (s, 1H), 7.22 (s, 1H), 8.83 (s, 1H). *m/z* 342 $(M+H)^+$.

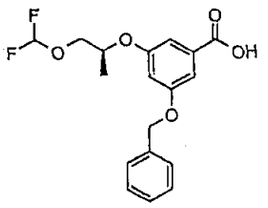
3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



DIPEA (0.198 mL, 1.14 mmol) was added to a mixture of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoic acid (0.1 g, 0.28 mmol), 3-amino-1-methyl pyrazole (39 mg, 0.4 mmol) and HATU (0.227 g, 0.6 mmol) in DMF (3 mL) and stirred at RT for 20 hours. Ethyl acetate (30 mL) was added and the mixture washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give the desired compound (0.1 g).

^{1}H NMR δ ($CDCl_3$): 1.36 (d, 3H), 3.68 (s, 3H), 3.82-3.95 (m, 2H), 4.48 (sex, 1H), 5.00 (s, 2H), 6.19 (t, 1H), 6.63 (s, 1H), 6.73 (s, 1H), 6.93 (s, 1H), 7.03 (s, 1H), 7.28 (m, 1H), 7.35 (m, 5H), 8.59 (s, 1H). *m/z* 432 $(M+H)^+$.

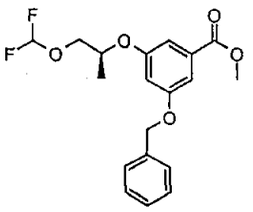
3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoic acid



Lithium hydroxide monohydrate (19 mg, 0.45 mmol) in water (2 mL) was added to methyl 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoate (0.11 g, 0.3 mmol) in THF (4 mL) and the mixture stirred at RT for 20 hours. The THF was removed *in vacuo* and the aqueous layer adjusted to pH3 with citric acid then extracted into ethyl actetate (2 x 30 mL). The organics were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the desired compound (0.1 g).

^{1}H NMR δ (d_6-DMSO): 1.27 (d, 3H), 4.00 (m, 2H), 4.75 (sextet, 1H), 5.15 (s, 2H), 6.72 (t, 1H), 7.08 (t, 1H), 7.16 (t, 1H), 7.41 (m, 5H), 12.95 (s, 1H). *m/z* 351 $(M+H)^+$.

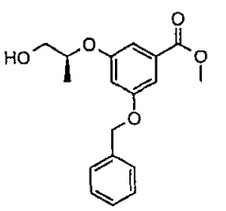
Methyl 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-[(phenylmethyl)oxy]benzoate



2-(Fluorosulphonyl)difluoroacetic acid (0.239 mL, 2.31 mmol) was added dropwise, with stirring, to a degassed mixture of methyl 3-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-5-[(phenylmethyl)oxy]benzoate (0.73 g, 2.31 mmol) and copper (I) iodide (88 mg, 0.46 mmol) in acetonitrile (10 mL) at 45°C. The reaction was stirred at 45°C for 24 hours. The solvent was removed *in vacuo* and ethyl acetate (30 mL) added. The organics were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-30% ethyl acetate in isohexane, to give the desired compound (0.11 g).

^{1}H NMR δ ($CDCl_3$): 1.37 (d, 3H), 3.93 (s, 3H), 4.00 (m, 2H), 4.63 (sextet, 1H), 5.10 (s, 2H), 6.28 (t, 1H), 6.77 (t, 1H), 7.28 (t, 1H), 7.41 (m, 6H). *m/z* 367 $(M+H)^+$.

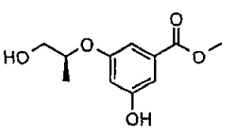
Methyl 3-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-5-[(phenylmethyl)oxy]benzoate



Benzyl bromide (1.89 g, 7.20 mmol) was added to a mixture of methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate (1.55 g, 6.86 mmol) and potassium carbonate (1.89 g, 0.014 mol) in DMF (16 mL) and the reaction stirred at RT for 20 hours. Ethyl acetate (40 mL) was added and the mixture washed with water (40 mL), saturated sodiumbicarbonate solution (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a red oil which was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give the desired compound (1.7 g).

^{1}H NMR δ ($CDCl_3$): 1.30 (d, 3H), 1.95 (m, 1H), 3.76 (m, 2H), 3.92 (s, 3H), 4.53 (m, 1H), 5.11 (s, 2H), 6.78 (t, 1H), 7.25 (m, 1H), 7.32 (m, 1H), 7.45 (m, 5H). *m/z* 317 $(M+H)^+$.

Methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate



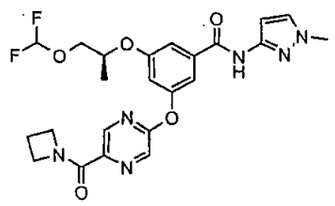
Trimethylsilyl iodide (115 mL, 0.79mol) was added to a solution of methyl 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate (38.01 g, 0.158mol) in acetonitrile (500 mL) and stirred for 24 hours. Methanol (300 mL) was added and the reaction stirred for 10 mins. 10% w/v Aqueous sodium thiosulfate pentahydrate (100 mL) was added to the mixture and stirred for 20 mins. The reaction mixture was neutralised with saturated aqueous sodium bicarbonate solution, the organic solvents removed *in vacuo*, and the product extracted into ethyl acetate (4 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. The crude material was crystallised from ethyl acetate to give the title compound (16.80 g).

ethyl acetate (50 mL) and water (50 mL), the organic layer washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The residue was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane, to give the desired compound (102 mg).

^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.28 (quin, 2H), 3.68 (s, 3H), 3.90 (mult, 2H), 4.17 (t, 2H), 4.54 (sextet, 1H), 4.63 (t, 2H), 6.19 (t, 1H), 6.71 (t, 1H), 6.73 (s, 1H), 7.06 (s, 1H), 7.22 (mult, 2H), 7.30 (mult, 1H), 8.04 (d, 1H), 8.24 (d, 1H), 8.84 (s, 1H); *m/z* 502 $(M+H)^+$

The preparation of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine were described earlier.

Example 18: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

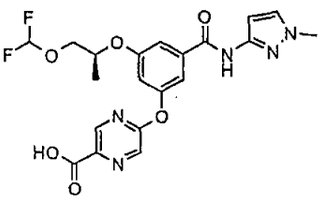


DIPEA (0.41 mL, 2.33 mmol) was added to a mixture of 5-[(3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (0.27 g, 0.58 mmol), azetidine hydrochloride (109 mg, 1.17 mmol) and HATU (466 mg, 1.22 mmol) in DMF (5 mL) and stirred at RT for 24 hours. Ethyl acetate (40 mL) was added and the organics washed with water (2 x 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. The residue was chromatographed on silica, eluting with 0-5% methanol in ethyl acetate, to give the desired compound (124 mg).

^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.30 (quin, 2H), 3.65 (s, 3H), 3.90 (m, 2H), 4.18 (t, 2H), 4.53 (sextet, 1H), 4.61 (t, 2H), 6.19 (t, 1H), 6.73 (d, 1H), 6.84 (t, 1H), 7.18 (m, 2H), 7.28 (s, 1H), 8.25 (s, 1H), 8.76 (s, 1H), 9.14 (s, 1H); *m/z* 503 $(M+H)^+$.

The preparation of 5-[(3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid is described below:

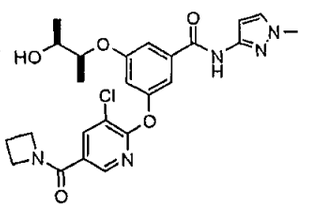
5-[(3-({(1*S*)-2-[(Difluoromethyl)oxy]-1-methylethyl}oxy)-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid



A mixture of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (220 mg, 0.64 mmol), methyl 5-chloropyrazine-2-carboxylate (112 mg, 0.64 mmol) and potassium carbonate (178 mg, 1.29 mmol) in acetonitrile (5 mL) was stirred in a 'Biotage initiator Microwave' at 160°C for 4 hours. The solvent was removed *in vacuo* and water (20 mL) added. The mixture was adjusted to pH3 with 1M citric acid and extracted into ethyl acetate (2 x 50 mL). The combined organics were washed with water (20 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil (0.19 g) which appeared to be a mixture of the acid and methyl ester. Lithium hydroxide monohydrate (26 mg, 0.60 mmol) in water (3 mL) was added to the mixture of acid and ester (0.19 g, 0.4 mmol) in THF (6 mL) and the mixture stirred at RT for 72 hours. The organics were removed *in vacuo* and the residue adjusted to pH3 with 1M citric acid, twice extracted into ethyl actetate and the combined organics, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the desired compound as a yellow solid (0.17 g).
m/z 464 $(M+H)^+$

The preparation of 3-({(1*S*)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier.

Example 19: 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1)



A solution of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (95 mg, 0.44 mmol), a mixture of 3-hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) (129 mg, 0.42 mmol) and potassium carbonate (146 mg, 1.05 mmol) in acetonitrile (3 mL) was heated in a microwave reactor at 160°C for 5 hours. The acetonitrile was removed *in vacuo* and the residue dissolved in ethyl acetate (25 mL). The organic solution was washed with water (25 mL), brine (25 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on alumina, eluting with a gradient of 0-5% methanol in ethyl acetate, to give the required product (56 mg).

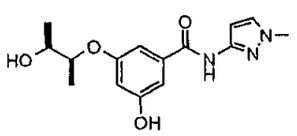
^{1}H NMR δ ($CDCl_3$): 1.18 (m, 6H), 2.32 (m, 3H), 3.66 (s, 3H), 3.79 (quin, 1H), 4.15 (m, 3H), 4.28 (t, 2H), 6.72 (d, 1H), 6.85 (t, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.29 (s, 1H), 8.08 (m, 1H), 8.15 (m, 1H), 9.10 (s, 1H); *m/z* 501 $(M+H)^+$

This mixture of diasteromers were separated by chiral preparatory HPLC on a Chiralpak IA (250mm x 20mm) No. EG014 column, eluting with a mixture of isohexane / ethyl acetate / acetic acid / triethylamine (40 / 60 / 0.2 / 0.1) to give the first eluted isomer (43 mg), **Example 19a**, and the second eluted isomer (40 mg), **Example 19b**.

The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine was described earlier.

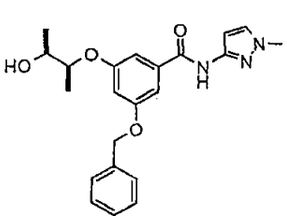
The preparation of 3-hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) is described below:

3-Hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1)



A solution of a mixture of 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1:1) (1.26 g, 3.19 mmol) and 10% by weight palladium on carbon (0.13 g) in ethanol (50 mL) was allowed to stir at RT under a hydrogen atmosphere for 16 hours. The solution was filtered through Celite® and washed through with methanol (100 mL). The solution was concentrated *in vacuo* to give the desired compound (1.03g). ^{1}H NMR δ (d_6-DMSO): 1.09 (d, 3H), 1.17 (d, 3H), 3.76 (m, 1H), 3.78 (s, 3H), 4.34 (quin, 1H), 6.48 (t, 1H), 6.56 (d, 1H), 6.93 (t, 1H), 7.05 (t, 1H), 7.60 (d, 1H), 9.66 (s, 1H), 10.67 (s, 1H); *m/z* 306 $(M+H)^+$

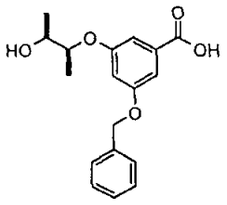
3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1:1)



A solution of a mixture of 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (1:1) (2.50 g, 7.92 mmol), 1-methyl-1*H*-pyrazol-3-amine (1.54 g, 15.8 mmol), HATU (3.92 g, 10.3 mmol) and DIPEA (2.76 mL, 15.8 mmol) in DMF (15 mL) was stirred at RT and under ambient atmosphere for 16 hours. Water (150 mL) was added and the solution extracted with ethyl acetate (250 mL). The ethyl acetate layer was washed with brine and dried ($MgSO_4$), and evaporated to a residue which was

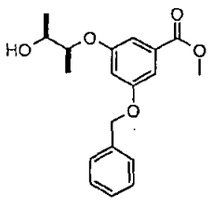
chromatographed on silica, eluting with 50% ethyl acetate in hexane, to give the desired product (1.26 g). ^{1}H NMR δ ($CDCl_3$): 1.17 (s, 3H), 1.18 (s, 3H), 2.44 (d, 1H), 3.70 (s, 3H), 3.77 (m, 1H), 4.10 (quin, 1H), 4.99 (s, 2H), 6.64 (t, 1H), 6.75 (d, 1H), 6.96 (t, 1H), 7.03 (t, 1H), 7.22 (d, 1H), 7.31 (m, 5H), 8.68 (s, 1H); *m/z* 396 $(M+H)^+$

3-{[(1*R*,2*R*)-2-Hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid and 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (1:1)



To a solution of a mixture of methyl 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate and methyl 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate (1:1) (2.52 g, 7.63 mmol) in THF (40 mL) was added a solution of lithium hydroxide monohydrate (0.80 g, 19.07 mmol) in water (10 mL). The mixture was allowed to stir at RT for 16 hours. The THF was removed *in vaccuo* and the resulting solution was partitioned between water (100 mL) and ethyl acetate (250 mL). The ethyl acetate layer was washed with brine (50 mL) and dried ($MgSO_4$). The aqueous layer was then adjusted to pH 7 by addition of 1M hydrochloric acid and extracted with ethyl acetate (75 mL). The ethyl acetate layer was washed with brine and dried ($MgSO_4$). The ethyl acetate layers were combined and evaporated to give the required product (2.50 g). ^{1}H NMR δ ($CDCl_3$): 1.18 (s, 3H), 1.20 (s, 3H), 3.80 (quin, 1H), 4.14 (quin, 1H), 5.01 (s, 2H), 6.72 (t, 1H), 7.21 (m, 1H), 7.32 (m, 6H).

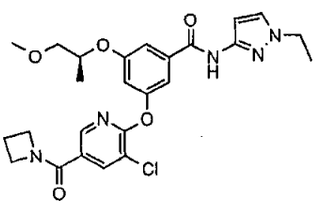
Methyl 3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate and methyl 3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-[(phenylmethyl)oxy]benzoate (1:1)



A solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (3.00 g, 11.61 mmol), (2*R*,3*S*)-2,3-dimethyloxirane (3.04 mL, 34.8 mmol), and potassium carbonate (4.02 g, 29.0 mmol) in acetonitrile (60 mL) was heated in a microwave reactor at 150°C for 3 hours. The acetonitrile was removed *in vacuo* and the residual oil dissolved in ethyl acetate (50 mL), washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and evaporated to a residual oil. The residue was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (2.52 g). ^{1}H NMR δ ($CDCl_3$): 1.17 (d, 6H), 3.82 (s, 3H), 4.04 (q, 2H), 4.99 (s, 2H), 6.67 (t, 1H), 7.14 (s, 1H), 7.30 (m, 6H); *m/z* 330 $(M-H)^-$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

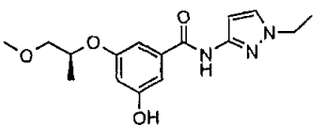
Example 20: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-*N*-(1-ethyl-1*H*-pyrazol-3-yl)-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide



A solution of *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide (128 mg, 0. 4 mmol) and the 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (111 mg, 0.48 mmol) in acetonitrile (2 mL) containing potassium carbonate (111 mg, 0.8 mmol) was heated in a microwave reactor at 160°C for 6 hours. The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure and purified by chromatography on silica, eluting with 50-100% ethyl acetate in hexane to give the required product as a white foam (176 mg).
^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 1.41 (t, 3H), 2.32 (quin, 2H), 3.35 (s, 3H), 3.49 (m, 2H), 4.02 (q, 2H), 4.17 (t, 2H), 4.30 (t, 2H), 4.56 (q, 1H), 6.76 (d, 1H), 6.88 (t, 1H), 7.18 (s, 1H), 7.28 (d, 1H), 7.32 (t, 1H), 8.09 (d, 1H), 8.18 (d, 1H), 8.65 (s, 1H); *m/z* 514 $(M+H)^+$

The preparation of *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide is described below:

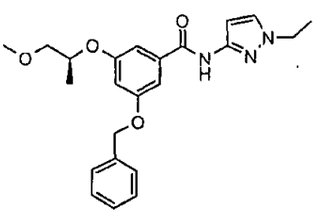
N-(1-Ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide



10% Palladium on carbon (1.9 g, 50% wet) was added under argon to *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-[(phenylmethyl)oxy]benzamide (19.1 g, 46.7 mmol) in dry THF (100 mL) and ethanol (100 mL). The reaction mixture was degassed, placed under a hydrogen balloon and stirred for 16 hours. The mixture was filtered through diatomaceous earth and the filtrate was evaporated to give a brown oil. The residue was purified by column chromatography on silica, eluting with 40-65% ethyl acetate in hexanes, to give the desired product as a clear oil which crystallised on standing (11.35 g).

^{1}H NMR δ ($CDCl_3$): 1.21 (d, 6H), 1.38 (t, 3H), 3.32 (s, 3H), 3.39 - 3.51 (m, 3H), 3.98 (q, 2H), 4.44 - 4.51 (m, 1H), 6.54 (s, 1H), 6.72 (d, 1H), 6.92 (s, 2H), 7.26 (d, 1H), 8.18 (s, 1H), 8.85 (s, 1H); *m/z* 320 $(M+H)^+$ 318 $(M-H)^-$

N-(1-Ethyl-1*H*-pyrazol-3-yl)-3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-[(phenylmethyl)oxy]benzamide



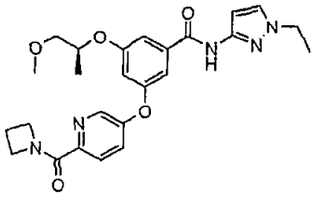
HATU (23.5 g, 61.83 mmol) was added to 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (16.28 g, 51.53 mmol) followed by addition of DMF (140 mL) and cooled to 0°C. 1-Ethyl-1*H*-pyrazol-3-amine (6.86 g, 61.8 mmol) was added followed by DIPEA (21.3 mL) and the reaction stirred under argon, at 0°C, for 3 hours. The solvent volume was reduced and the residue was dissolved in ethyl acetate (500 mL), washed with citric acid (200 mL), sodium hydrogen carbonate solution (150 mL) and saturated brine solution (2 x 150 mL). The organic layer was separated and dried ($MgSO_4$),

filtered and evaporated. Purification by column chromatography on silica, eluting with 10-50% ethyl acetate in hexanes, afforded the title compound as a pale yellow oil (19.1 g). ^{1}H NMR δ ($CDCl_3$): 1.23 (d, 3H), 1.38 (t, 3H), 3.33 (s, 3H), 3.42 (dd, 1H), 3.50 (dd, 1H), 3.97 (q, 2H), 4.49 (sextet, 1H), 4.99 (s, 2H), 6.66 (t, 1H), 6.75 (d, 1H), 6.98 (s, 1H), 7.02 (s, 1H), 7.26 (d, 1H), 7.28 - 7.37 (m, 5H), 8.58 (s, 1H); *m/z* 410 $(M+H)^+$

The preparation of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid was described earlier.

The preparation of 1-ethyl-1*H*-pyrazol-3-amine is described in the literature [*Chem. Heterocycl. Compd. (Engl. Transl.)*,11, **1975**, 212].

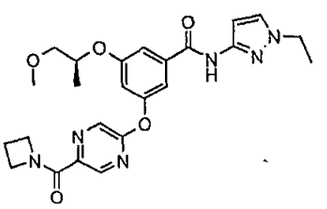
Example 21: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-*N*-(1-ethyl-1*H*-pyrazol-3-yl)-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide



A mixture of *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide (0.128g, 0.4 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (116 mg, 0..48 mmol), cesium carbonate (392 mg, 1.2 mmol) and bromotris(triphenylphosphine)copper(I) (38 mg, 0.04 mmol) in DMA (5 mL) was stirred in a microwave reactor at 160°C for 4 hours. The product was dissolved in ethyl acetate (20 mL) and water (15 mL) and the layers separated. The organic layer washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil which was chromatographed on silica, eluting with a gradient of 70-100% ethyl acetate in hexane to give the desired material as a clear foam (76 mg). ^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 1.40 (t, 3H), 2.29 (quin, 2H), 3.34 (s, 3H), 3.42 - 3.53 (m, 2H), 4.01 (q, 2H), 4.18 (t, 2H), 4.54 (q, 1H), 4.64 (t, 2H), 6.74 (t, 2H), 7.04 (s, 1H), 7.22 (s, 1H), 7.27 (d, 1H), 7.30 (d, 1H), 8.04 (d, 1H), 8.25 (d, 1H), 8.47 (s, 1H); *m/z* 480 $(M+H)^+$

The preparation of *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine was described earlier.

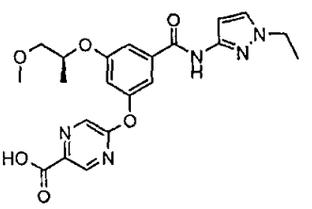
Example 22: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-*N*-(1-ethyl-1*H*-pyrazol-3-yl)-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide



HATU (304 mg, 0.80 mmol) was added to 5-[(3-{[(1-ethyl-1*H*-pyrazol-3-yl)amino]carbonyl}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)oxy]pyrazine-2-carboxylic acid (0.4 mmol) and azetidine hydrochloride (75 mg, 0.89 mmol) in DMF (5 mL) followed by addition of DIPEA (0.278 mL, 1.6 mmol) and the reaction was stirred for 16 hours. The reaction mixture was added to ethyl acetate (20 mL), the organic solution washed with water (10 mL), 2N citric acid (10 mL), saturated aqueous sodium hydrogencarbonate (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure to a gum. The residue was purified by chromatography on silica, eluting with 70-100% ethyl acetate in hexane, to give the desired compound as a white foam (98 mg). ^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 1.40 (t, 3H), 2.31 (quin, 2H), 3.34 (s, 3H), 3.43 - 3.54 (m, 2H), 4.01 (q, 2H), 4.19 (t, 2H), 4.54 (q, 1H), 4.62 (t, 2H), 6.73 (d, 1H), 6.87 (t, 1H), 7.18 (t, 1H), 7.27 (d, 1H), 7.30 (t, 1H), 8.26 (d, 1H), 8.49 (s, 1H), 8.78 (d, 1H); *m/z* 481 $(M+H)^+$

The preparation of 5-[(3-{[(1-ethyl-1*H*-pyrazol-3-yl)amino]carbonyl}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)oxy]pyrazine-2-carboxylic acid is described below:

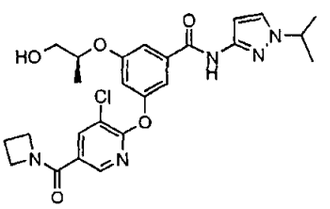
5-[(3-{[(1-Ethyl-1*H*-pyrazol-3-yl)amino]carbonyl}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)oxy]pyrazine-2-carboxylic acid



A solution of *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide (128 mg, 0.4 mmol) and the methyl-5-chloropyrazine-2-carboxylate (83 mg, 0.48 mmol) in acetonitrile (2 mL), containing potassium carbonate (111 mg, 0.8 mmol), was heated in a microwave reactor at 160°C for 6 hours. The reaction mixture was dissolved in water (10 mL), acidified with 2N citric acid and extracted with ethyl acetate (5 x 20 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure to give the desired material a yellow solid (164 mg), which was used without purification in the next step. *m/z* 442 $(M+H)^+$

The preparation of *N*-(1-ethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide was described earlier.

Example 23: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]benzamide



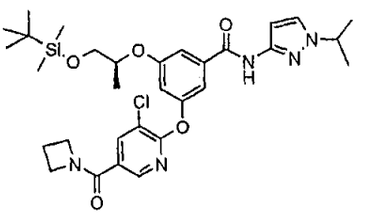
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]benzamide (142 mg, 0.23 mmol) in methanol (2 mL) was stirred with 3.5M hydrochloric acid (0.2 mL, 0.68 mmol) for 1 hour. The solution was neutralised with saturated sodium bicarbonate solution and the organic solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 10 mL), dried ($MgSO_4$), filtered

and the solvent removed under reduced pressure. The residue was purified by chromatography on silica, eluting with 75-100% ethyl acetate in hexane, to give the required product as a white foam (99 mg).

^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 1.41 (d, 6H), 2.32 (quin, 2H), 3.67 - 3.71 (m, 2H), 4.17 (t, 2H), 4.26 - 4.35 (m, 3H), 4.52 (q, 1H), 6.73 (s, 1H), 6.87 (s, 1H), 7.19 (s, 1H), 7.30 (s, 1H), 7.32 (s, 1H), 8.10 (s, 1H), 8.18 (s, 1H), 8.56 (s, 1H); *m/z* 514 $(M+H)^+$

The preparation of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]benzamide is described below:

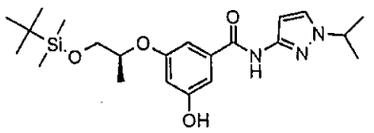
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]benzamide



A solution of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]benzamide (103 mg, 0.24 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (66 mg, 0.29 mmol) in acetonitrile (2 mL), containing potassium carbonate (66 mg, 0.48 mmol), was heated in a microwave reactor at 160°C for 6 hours. The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure and purified by chromatography on silica, eluting with 50-100% ethyl acetate in hexane, to give the required product as a white foam (142 mg).

m/z 628 $(M+H)^+$

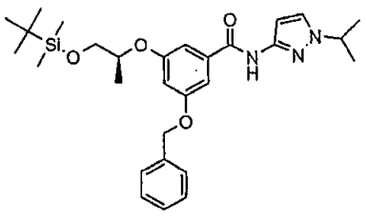
3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]benzamide



A solution of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]-5-[(phenylmethyl)oxy]benzamide (1.97 g, 3.77 mmol) and THF (70 mL) was evacuated and purged with Argon (x3). Palladium on carbon (10% w/w, 400 mg) was added and reaction mixture was evacuated and finally purged with hydrogen gas. Reaction mixture was left to stir at ambient temperature under hydrogen for 16 hours. The palladium on carbon was filtered off and concentrated *in vacuo* to give the product as a colourless oil (1.58 g, 97%).

^{1}H NMR δ ($CDCl_3$): 0.02 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.27 (d, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 3.63 (dd, 1H), 3.77 (dd, 1H), 4.41 (m, 1H), 6.60 (s, 1H), 6.81 (s, 1H), 7.00 (s, 1H), 7.07 (s, 1H), 7.38 (s, 1H), 8.78 (br. s, 1H); *m/z* 434 $(M+H)^+$, 432 $(M-H)^-$.

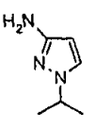
3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-[1-(1-methylethyl)-1*H*-pyrazol-3-yl]-5-[(phenylmethyl)oxy]benzamide



DIPEA (3.11 mL, 18.03 mmol) was added to a solution of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (3.00 g, 7.21 mmol), HATU (3.12 g, 8.21 mmol) and 1-(1-methylethyl)-1*H*-pyrazol-3-amine (1.13 g, 9.01 mmol) in DMF (10 mL). The resulting mixture was stirred at ambient temperature for 16 hours. The DMF was removed *in vacuo*. The solvent was evaporated and the residue was dissolved in 5%w/v citric acid (50 mL) and ethyl acetate (30 mL) and diethyl ether (30 mL) and the organic layer was further washed with saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL). The organic layer was separated,

then dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography, eluting with 1:4 to 1:3 ethyl acetate:hexanes, afforded the title compound as a colourless oil (2.40 g, 65%). ^{1}H NMR δ ($CDCl_3$): 0.01 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.24 (d, 3H), 1.49 (s, 3H), 1.51 (s, 3H), 3.64 (dd, 1H), 3.78 (dd, 1H), 4.39 (m, 1H), 4.46 (m, 1H), 5.09 (s, 2H), 6.70 (s, 1H), 6.78 (s, 1H), 7.02 (s, 1H), 7.08 (s, 1H), 7.35 (m, 6H), 8.32 (br. s, 1H); *m/z* 524 $(M+H)^+$, 522 $(M-H)^-$.

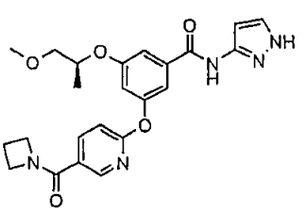
1-(1-Methylethyl)-1*H*-pyrazol-3-amine



2-Chloroacrylonitrile (3.41 mL, 42.59 mmol) was added at RT to a stirring solution of *N*-isopropylhydrazine hydrochloride (4.71 g, 42.6 mmol), potassium carbonate (11.8 g, 85.2 mmol) in water (50 mL). The reaction was warmed to 45°C for 4 hours before cooling back to RT. The aqueous layer was then extracted with ethyl acetate (5 x 30 mL) and the combined organic layers were dried ($MgSO_4$), treated with activated charcoal, filtered and evaporated. The residue was purified by chromatography, eluting with 67%-100% ethyl acetate in hexanes, to afford the title compound (3.08 g, 58%) as a 6:1 mixture of authentic product to regioisomeric product as an oil. The material was used without further purification. ^{1}H NMR δ ($CDCl_3$): 1.42 (m, 6H), 3.58 (br. s, 2H), 4.25 (sept, 1H), 5.58 (d, 1H), 7.15 (d, 1H).

The preparation of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid was described earlier.

Example 24: 3-{[5-(Azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-1*H*-pyrazol-3-ylbenzamide

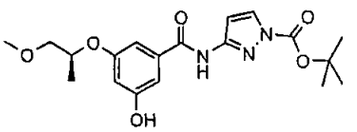


A solution of 1,1-dimethylethyl 3-{[(3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)carbonyl]amino}-1*H*-pyrazole-1-carboxylate (157 mg, 0.4 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (95 mg, 0.48 mmol) in acetonitrile (2 mL), containing potassium carbonate (111 mg, 0.8 mmol), was heated in a microwave reactor at 160°C for 6 hours. The reaction mixture was filtered and the filtrate evaporated to dryness under reduced pressure and purified by chromatography on silica, eluting with 50-100% ethyl acetate in hexane to give a product which was further purified by chromatography on silica, eluting with 0-8% methanol in ethyl acetate, to give the required product as a white foam (21 mg).

^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.30 (quin, 2H), 3.33 (s, 3H), 3.42 - 3.54 (m, 2H), 4.12 - 4.29 (m, 4H), 4.54 (q, 1H), 6.77 (s, 1H), 6.81 (t, 1H), 6.97 (d, 1H), 7.20 (s, 1H), 7.27 (s, 1H), 7.33 (d, 1H), 8.01 (d, 2H), 8.28 (d, 1H), 10.27 (s, 1H); *m/z* 452 $(M+H)^+$

The preparation of 1,1-dimethylethyl 3-{[(3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)carbonyl]amino}-1*H*-pyrazole-1-carboxylate is described below:

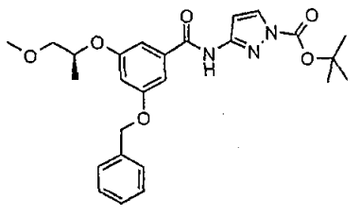
1,1-Dimethylethyl 3-{[(3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)carbonyl]amino}-1*H*-pyrazole-1-carboxylate



A solution of 1,1-dimethylethyl 3-[({3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-[(phenylmethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate (23 g, 47.8 mmol) in THF (140 mL) and ethanol (140 mL) was evacuated and purged with nitrogen (x3). 10% Palladium on carbon (2.3 g; 10% w/w) was added and reaction mixture was evacuated and finally purged with hydrogen gas. The reaction mixture was left to stir at RT under a hydrogen balloon for 16 hours. The palldium on carbon was filtered through diatomaceous earth and the filtrate concentrated *in vacuo* to give a white foam (18 g, 97%).

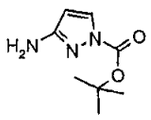
^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 1.55 (s, 9H), 3.25 (s, 3H obscured by water peak), 3.4-3.5 (m, 2H), 4.7 (m, 1H), 6.5 (s, 1H), 6.95 (d, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 8.2 (d, 1H), 9.65 (s, 1H), 11.2 (s, br, 1H); *m/z* 392 $(M+H)^+$

1,1-Dimethylethyl 3-[({3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-[(phenylmethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate



DIPEA (28.5 mL, 164 mmol) was added to a suspension of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (20.7 g, 65.6 mmol), HATU (31.2 g, 82.0 mmol) and 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate (15.0 g, 82.0 mmol) in DMF (30 mL) and the reaction mixture stirred for 16 hours at RT. Water (250 mL) was added and the reaction mixture extracted with diethyl ether (3 x 150 mL). The organic layer was washed with saturated brine solution and dried ($MgSO_4$). The filtrate was concentrated *in vacuo* and the residue crystallised on standing. The crystals were washed with isohexane to give to give the desired material as yellow crystals (23.4 g; 73%). *m/z* 482 $(M+H)^+$.

1,1-Dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate

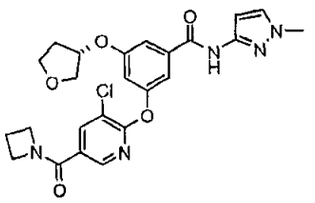


1*H*-Pyrazol-3-amine (428 mg, 5.15 mmol) was dissolved in DMF (5 mL) at 0°C and treated with sodium hydride (206 mg, 5.15 mmol) followed by stirring for a further 30 min. Warmed di-tert-butyl dicarbonate (1.12 g, 5.15 mmol) was then slowly added via syringe over 5 min and the reaction was allowed to warm to room temperature and stirred for a further 2 h. The reaction was taken up in saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate (100 mL). The organic layer was separated then dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography (eluting with 1:1 ethyl acetate:hexanes to neat ethyl acetate) afforded the title compound (117 mg) as a white solid. ^{1}H NMR δ ($CDCl_3$): 1.62 (s, 9H), 4.00 (br. s, 2H), 5.81 (d, 1H), 7.82 (d, 1H)

1,1-Dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate was also made by reacting a solution of 1*H*-pyrazol-3-amine in THF (1 g in approximately 15.6 mL) with NaHMDS

(2M in THF, 1.05 equivalents) then adding a solution of di-tert-butyl dicarbonate (1 equivalent) in THF (approximately 1g of dicarbonate in 1.9 mL) and stirring at RT. The resulting material was crystallised from a mixture of ethyl acetate and isohexane.
The preparation of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid was described earlier.

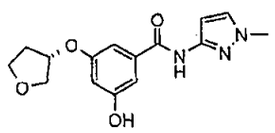
Example 25: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



A mixture of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (80 mg, 0.26 mmol), 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (61 mg, 0.26 mmol) and caesium carbonate (172 mg, 0.53 mmol) in acetonitrile (3 mL) was stirred in a Smith Creator microwave at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue. The organic phase was washed with water (20 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-10% methanol in DCM, to give the title compound as a yellow foam (52 mg).
^{1}H NMR δ ($CDCl_3$): 2.16 - 2.24 (2H, m), 2.34 - 2.44 (4H, m), 3.78 (3H, s), 3.89 - 4.01 (4H, m), 4.24 (2H, t), 4.37 (2H, t), 4.99 (1H, s), 6.80 (1H, s), 6.89 (1H, s), 7.23 (1H, s), 7.30 (2H, d), 8.16 (1H, s), 8.24 (1H, s), 8.73 (1H, s); *m/z* 498 $(M+H)^+$.

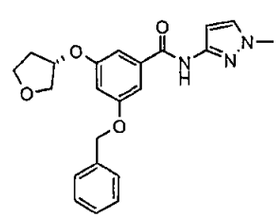
The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine was described earlier.
The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide is described below:

3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



N-(1-Methyl-1*H*-pyrazol-3-yl)-3-[(phenylmethyl)oxy]-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (453 mg, 1.15 mmol) was dissolved in ethanol (5 mL) and ammonium formate (182 mg, 2.88 mmol) was added in one portion. The reaction was blanketed with argon and 10% palladium on activated carbon (30 mg) was added. This mixture was heated to 140°C for 10 minutes in a Smith Creator microwave. The catalyst was filtered off and the volatiles removed *in vacuo* to give the title product as a white solid (339 mg).
^{1}H NMR δ ($CDCl_3$): 2.06 - 2.14 (1H, m), 2.15 - 2.22 (1H, m), 3.72 - 3.73 (3H, s), 3.84 - 3.89 (1H, m), 3.92 - 3.98 (3H, m), 4.88 (1H, m), 6.53 (1H, t), 6.78 (1H, d), 6.89 (1H, s), 6.95 (1H, s), 7.28 (1H, d), 9.27 (1H, s); *m/z* 304 $(M+H)^+$.

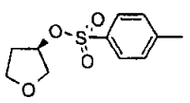
N-(1-Methyl-1*H*-pyrazol-3-yl)-3-[(phenylmethyl)oxy]-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



A suspension of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (450 mg, 1.39 mmol), (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (507 mg, 2.09 mmol) and potassium carbonate (481 mg, 3.48 mmol) in acetonitrile (5 mL) was stirred in a Smith Creator microwave at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate added. The organics were washed with water (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow foam which was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in *iso*-hexane, to give the title compound as a white foam (452 mg).

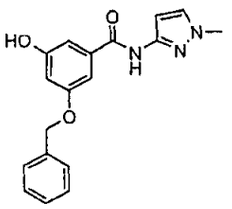
^{1}H NMR δ ($CDCl_3$): 2.09 - 2.14 (1H, m), 2.14 - 2.24 (1H, m), 3.68 (3H, s), 3.86 - 3.91 (1H, m), 3.94 - 3.98 (3H, m), 4.89 (1H, s), 5.03 (2H, s), 6.64 (1H, t), 6.85 (1H, s), 6.96 (1H, d), 7.07 (1H, t), 7.27 (1H, m), 7.33 - 7.41 (5H, m), 9.31 (1H, s); *m/z* 394 $(M+H)^+$.

(3*R*)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate



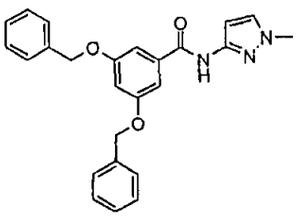
4-Toluene sulfonyl chloride (1.65 g, 8.63 mmol) was added to a solution of *R*-3-hydroxytetrahydrofuran (0.8 g, 9.08 mmol) and pyridine (0.88 mL, 10.9 mmol) in DCM (15 mL). The reaction was stirred at RT for 72 hours. Water (10 mL) and 1M hydrochloric acid (1 mL) were added and the mixture extracted with DCM (15 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give a yellow oil which was chromatograped on silica, eluting with a gradient of 0-50% ethyl acetate in isohexane, to give the desired compound (1.0 g). ^{1}H NMR δ ($CDCl_3$): 2.13 (m, 2H), 2.47 (s, 3H), 3.80-3.95 (m, 4H), 5.15 (m, 1H), 7.37 (d, 2H), 7.81 (d, 2H).

3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



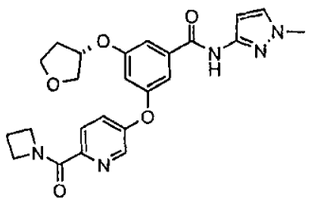
A suspension of *N*-(1-methyl-1*H*-pyrazol-3-yl)-3,5-bis[(phenylmethyl)oxy]benzamide (1.0 g, 2.42 mmol) was dissolved in ethanol (12 mL) and ammonium formate (229 mg, 3.63 mmol) was added in one portion. The reaction was blanketed with argon and 10% palladium on activated carbon (10 mg) was added. This mixture was heated to 140°C for 5 minutes in a Smith Creator microwave. The catalyst was filtered off and the volatiles removed *in vacuo*, the residue was chromatographed on silica, eluting with a gradient of 30-100% ethyl acetate in *iso*-hexane, to give the title compound as a white solid (378 mg). ^{1}H NMR δ (d_6-DMSO): 3.78 (3H, s), 5.13 (2H, s), 6.55 - 6.57 (2H, m), 6.99 (1H, s), 7.17 (1H, s), 7.34 – 7.48 (5H, m), 7.60 (1H, d), 9.74 (1H, s), 10.70 (1H, s); *m/z* 324 $(M+H)^+$.

N-(1-Methyl-1*H*-pyrazol-3-yl)-3,5-bis[(phenylmethyl)oxy]benzamide



Oxalyl chloride (7.71 mL, 89.7 mmol) was added dropwise to a suspension of 3,5-dibenzyloxybenzoic acid (20.0 g, 59.8 mmol) in DCM (0.5 L) under argon. The reaction was stirred at RT for 6 hours after which time the volatiles were removed *in vacuo*. The residue was taken up in DCM (300 mL) and a solution of 1-methyl-1*H*-pyrazol-3-amine (5.81 g, 59.8 mmol) in DCM (50 mL) was added dropwise. The resulting solution was stirred for 16 hours at RT after which time a precipitate had formed. The solid was isolated by filtration and recrystallised from ethanol to give the title compound as a white solid (14.8 g). ^{1}H NMR δ (d_6-DMSO): 3.84 (3H, s), 5.17 (4H, s), 6.59 (1H, d), 6.84 (1H, t), 7.33 - 7.46 (12H, m), 7.62 (1H, d), 10.83 (1H, s); *m/z* 414 $(M+H)^+$.

Example 26: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide

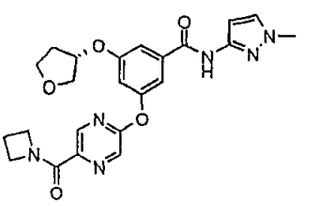


A mixture of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (80 mg, 0.26 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (64 mg, 0.26 mmol), bromotris(triphenylphosphine)copper(I) (49 mg, 0.05 mmol) and caesium carbonate (257 mg, 0.78 mmol) in acetonitrile (3 mL) was stirred in a Smith Creator microwave at 160°C for 6 hours. The solid was filtered off and the solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue. The organic phase was washed with water (20 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with a gradient of 0-10% methanol in DCM, to give the title compound as a colourless solid (58 mg). This

compound was crystallised from ethyl acetate and isohexane using vapour diffusion techniques. ^{1}H NMR δ ($CDCl_3$): 2.11 - 2.17 (1H, m), 2.20 - 2.29 (1H, m), 2.32 - 2.39 (2H, m), 3.78 (3H, s), 3.88 - 3.93 (1H, m), 3.96 - 4.02 (3H, m), 4.25 (2H, t), 4.71 (2H, t), 4.97 (1H, t), 6.73 (1H, t), 6.79 (1H, s), 7.11 (1H, s), 7.22 (1H, s), 7.27 - 7.30 (1H, m), 7.36 - 7.39 (1H, m), 8.12 (1H, d), 8.32 (1H, d), 8.73 (1H, s); *m/z* 464 $(M+H)^+$.

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine was described earlier.

Example 27: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide

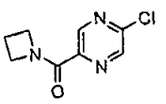


A mixture of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (80 mg, 0.26 mmol), 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (52 mg, 0.26 mmol) and caesium carbonate (172 mg, 0.53 mmol) in acetonitrile (3 mL) was stirred in a Smith Creator microwave at 160°C for 1 hr. The solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue. The organic phase was washed with water (20 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil which was chromatographed on silica eluting with a gradient of 0-10% methanol in DCM to give the title compound (36 mg, 31 %) as a white foam. This compound was crystallised from ethyl acetate and isohexane using vapour diffusion techniques. ^{1}H NMR δ ($CDCl_3$): 2.12 - 2.19 (1H, m), 2.21 - 2.28 (1H, m), 2.34 - 2.42 (2H, m), 3.75 (3H, s), 3.88 - 3.93 (1H, m), 3.98 - 4.02 (3H, m), 4.23 (2H, t), 4.69 (2H, t), 4.95 - 4.97 (1H, m), 6.80 (1H, d), 6.87 (1H, t), 7.23 (1H, d), 7.27 - 7.30 (1H, m), 7.28 - 7.30 (1H, m), 8.34 (1H, d), 8.84 (1H, d), 8.98 (1H, s); *m/z* 465 $(M+H)^+$.

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide was described earlier.

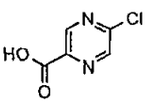
The preparation of 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine is described below:

2-(Azetidin-1-ylcarbonyl)-5-chloropyrazine



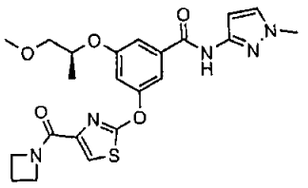
Oxalyl chloride (1.55 mL, 17.48 mmol), followed by DMF (2 drops), was added to a mixture of 5-chloropyrazine-2-carboxylic acid (2.31 g, 14.57 mmol) in DCM (40 mL). The reaction was stirred at RT for 2 hours after which time the volatiles were removed *in vacuo*. The residue was taken up DCM (40 mL) and azetidine (1.08 mL, 16.03 mmol) and triethylamine (4.46 mL, 32.06 mmol) added. The mixture was stirred at RT for 72 hours. The volatiles were removed *in vacuo* and ethyl acetate (100 mL) added to the residue. The organics were washed with water (100 mL), citric acid (50 mL), saturated sodium bicarbonate solution (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow solid. The residue was chromatographed on silica, eluting with a gradient of 50 -100% ethyl acetate in *iso*-hexane, to give the desired compound as a yellow solid (2.38 g). ^{1}H NMR δ ($CDCl_3$): 2.35 - 2.42 (2H, m), 4.26 (2H, t), 4.67 (2H, t), 8.52 (1H, d), 9.09 (1H, d); *m/z* 198 $(M+H)^+$.

5-Chloropyrazine-2-carboxylic acid



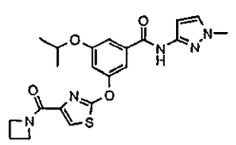
To a solution of methyl-5-chloropyrazine-2-carboxylate (120 mg, 0.70 mmol) in a mixture of acetonitrile (2 mL) and DMF (1 mL) was added lithium chloride (295 mg, 6.95 mmol). The suspension was heated to 160°C for 5 mins in a Smith creator microwave after which time the reaction was diluted with water (10 mL). Saturated sodium bicarbonate solution (20 mL) was added and the aqueous layered extracted twice with ethyl acetate (30 mL). The combined organics were discarded and the aqueous layer adjusted to pH 4 with 1N hydrochloric acid. The aqueous phase was extracted twice with ethyl acetate (20 mL) and the combined organics washed with water (2 x 20 mL), brine (10 mL) and dried ($MgSO_4$). The volatiles were removed to give the title compound as a colourless solid (68 mg). ^{1}H NMR δ ($CDCl_3$): 7.20 (1H, br s), 8.72 (1H, s), 9.21 - 9.21 (1H, m); *m/z* 157 $(M-H)^+$.

Example 28: 3-{[4-(Azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



Cesium carbonate (488 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (153 mg, 0.5 mmol) and 4-(azetidin-1-ylcarbonyl)-2-bromo-1,3-thiazole (206 mg, 0.75 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 150°C in a Biotage Initiator Microwave apparatus for 8 hours. The mixture was cooled to RT and pressure, poured onto water (75 mL) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired material (95 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.2 (m, 2H), 3.3 (s, 3H), 3.4-3.55 (m, 2H), 3.7 (s, 3H), 4.1 (t, 2H), 4.4 (t, 2H), 4.5 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.25 (s, 1H), 7.3 (s, 2H), 7.35 (s, 1H), 7.65 (s, 1H) and 8.8 (s, 1H); *m/z* 472 $(M+H)^+$.

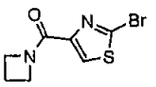
The following compound was prepared in an analogous fashion from 4-(azetidin-1-ylcarbonyl)-2-bromo-1,3-thiazole and 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

Example	Structure	m/z	NMR
28a		442 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.2 (m, 2H), 3.7 (s, 3H), 4.1 (m, 2H), 4.4 (m, 2H), 4.5 (m, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.25 (d, 2H), 7.3 (s, 1H), 7.65 (s, 1H) and 9.0 (s, 1H).

The preparation of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier

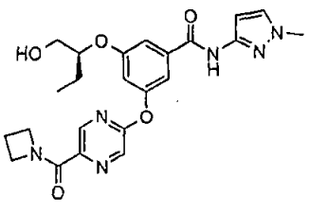
The preparation of 4-(azetidin-1-ylcarbonyl)-2-bromo-1,3-thiazole is described below:

4-(Azetidin-1-ylcarbonyl)-2-bromo-1,3-thiazole



To a solution of 2-bromothiazole-5-carboxylic acid (752 mg, 3.62 mmol) in DCM (10 mL) was slowly added oxalyl chloride (0.38 mL, 4.34 mmol) and then DMF (1 drop). The mixture was stirred for 4 hours, following which the organics were removed *in vacuo*, and the residues azeotroped with toluene (10 mL). The crude material was dissolved in DCM (10 mL) and slowly added to a stirred suspension of azetidine hydrochloride (404 mg, 4.34 mmol) and triethylamine (1.8 mL, 13 mmol) in DCM (25 mL). The mixture was stirred at RT for 2 hours before the organics were removed *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (25 mL), the organic layer washed with brine (25 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 40% ethyl acetate in *iso*-hexane, to give the desired compound (500 mg). ^1H NMR δ ($CDCl_3$): 2.3 (m, 2H), 4.15 (m, 2H), 4.6 (m, 2H) and 8.0 (s, 1H); *m/z* 249 $(M+H)^+$.

Example 29: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



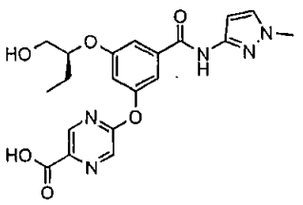
A solution of 5-[(3-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (12 mg, 0.03 mmol), azetidine hydrochloride (4 mg, 0.06 mmol), HATU (14 mg, 0.04 mmol) and DIPEA (0.02 mL, 0.11 mmol) in DMF (1 mL) was stirred at RT over the weekend. Water (15 mL) was added and the solution extracted with ethyl acetate (25 mL). The ethyl acetate layer was washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a residue which was chromatographed by preparative HPLC on C18 reversed phase, eluting with 5-95% acetonitrile (+0.2% TFA) in

water (+0.2% TFA), to give the required product along with 15% of a co-eluting impurity (5 mg). ^{1}H NMR δ ($CDCl_3$): 0.92 (t, 3H), 0.97 (t, 0.45H), 1.69 (quin, 2H), 1.76 (m, 0.3H), 2.34 (quin, 2H), 3.76 (m, 2H), 3.86 (s, 3H), 4.23 (t, 2H), 4.49 (sextet, 1H), 4.66 (t, 2H), 4.77 (m, 0.15H), 6.93 (t, 1H), 6.99 (d, 1H), 7.34 (s, 1H), 7.46 (s, 1H), 7.50 (s, 1H), 8.29 (s, 1H), 8.78 (s, 1H), 10.68 (s, 1H), 10.78 (s, 0.15H); *m/z* 468 $(M+H)^+$

The spectroscopic data is consistent with 15% of the following impurity 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(2*S*)-2-hydroxybutyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide.

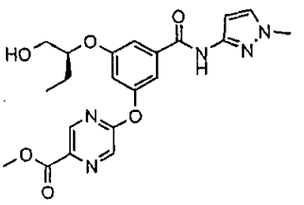
The preparation of 5-[(3-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid is described below:

5-[(3-{[(1*S*)-1-(Hydroxymethyl)propyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid



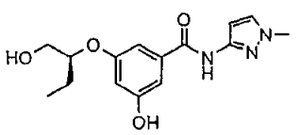
Lithium hydroxide monohydrate (6 mg, 0.14 mmol) in water (1 mL) was added to a solution of methyl 5-[(3-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate (25 mg, 0.06 mmol) in THF (1 mL). The mixture was allowed to stir at RT for 16 hours. The THF was removed *in vacuo* and the resulting solution was partitioned between water (10 mL) and ethyl acetate (25 mL), the ethyl acetate layer was washed with brine (10 mL) and dried ($MgSO_4$). The aqueous layer was then adjusted to pH 7 by addition of 1M hydrochloric acid and extracted with ethyl acetate (25 mL). The ethyl acetate layer was washed with brine (10 mL) and dried ($MgSO_4$). The ethyl acetate extracts were combined and evaporated to give the required product (12 mg). *m/z* 428.44 $(M+H)^+$

Methyl 5-[(3-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate



Methyl 5-chloropyrazine-2-carboxylate (104 mg, 0.60 mmol) and cesium carbonate (467 mg, 1.43 mmol) were added to a solution of 3-hydroxy-5-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (175 mg, 0.570 mmol), in acetonitrile (5 mL) and the mixture heated in a microwave reactor at 160°C for 330 minutes. The acetonitrile was removed *in vacuo* and the residue dissolved in ethyl acetate (25 mL), washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated to a residue which was chromatographed by preparative HPLC on C18 reversed phase, eluting with 5-95% acetonitrile (+0.2% TFA) in water (+0.2% TFA), to give the required product (41 mg). ^{1}H NMR δ ($CDCl_3$): 0.97 (t, 3H), 1.78 (quin, 2H), 3.82 (s, 3H), 3.91 (s, 3H), 4.52 (m, 3H), 4.66 (quin, 1H), 6.59 (t, 1H), 6.89 (d, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 8.19 (d, 1H), 8.79 (d, 1H), 9.86 (s, 1H); *m/z* 442 $(M+H)^+$

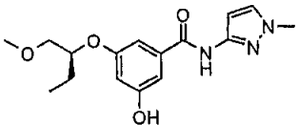
3-Hydroxy-5-{[(1*S*)-1-(hydroxymethyl)propyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



To a solution of 3-hydroxy-5-({(1*S*)-1-[(methyloxy)methyl]propyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (500 mg, 1.6 mmol) in acetonitrile (25 mL), iodotrimethylsilane (1.11 mL, 7.8 mmol) was added and the resulting mixture stirred for 16 hours. Saturated sodium hydrogencarbonate solution (10 mL) was added, the solution stirred for 10 mins, saturated aqueous sodium thiosulfate (5 mL) was added then the acetonitrile was removed *in vacuo*. The residual aqueous layer was extracted with ethyl acetate (3 x 40 mL) and the organic layers combined, dried ($MgSO_4$), filtered and evaporated and purified by column chromatography, eluting with 85% ethyl acetate in isohexane, to give the title compound as

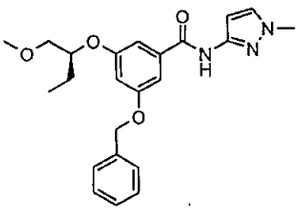
a colourless foam (405 mg). ^{1}H NMR δ (d_6-DMSO): 0.95 (t, 3H), 1.5-1.8 (m, 2H), 3.5 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 4.8 (t, 1H), 6.45 (s, 1H), 6.55 (s, 1H), 6.9 (s, 1H), 7.05 (s, 1H), 7.55 (s, 1H), 9.6 (s, 1H); *m/z* 306 $(M+H)^+$

3-Hydroxy-5-({(1*S*)-1-[(methyloxy)methyl]propyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



To a solution of 3-({(1*S*)-1-[(methyloxy)methyl]propyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (4.6 g, 11 mmol) in 1:1 THF:methanol (100 mL) was added 10% w/w palladium on carbon (450 mg) and the resulting mixture was stirred under an atmosphere of hydrogen for 6 hours. The atmosphere was replaced with argon and the mixture was filtered and evaporated to afford the title compound as a white solid (3.6 g). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 6.65 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.2 (m, 1H), 7.3 (s, 1H), 8.7 (s, 1H); *m/z* 320 $(M+H)^+$

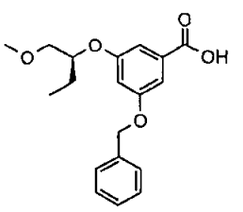
3-({(1*S*)-1-[(Methyloxy)methyl]propyl}oxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



To a solution of 3-({(1*S*)-1-[(methyloxy)methyl]propyl}oxy)-5-[(phenylmethyl)oxy]benzoic acid (4.75 g, 14.4 mmol) and 3-amino-1-methyl-1*H*-pyrazole (2.04 g, 21 mmol) in DMF (25 mL) was added HATU (8.53 g, 22.4 mmol) then DIPEA (7.0 mL, 40 mmol) and the resulting mixture was stirred for 16 hours. The mixture was partitioned between ethyl acetate (100 mL) and water (30 mL). The organic layer was separated, washed with 1N citric acid (30 mL), water (30 mL), saturated sodium

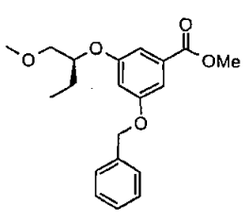
bicarbonate (30 mL), water (30 mL) and brine (30 mL) then dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography, eluting with 50% ethyl acetate in isohexane, to give the title compound as a colourless oil (4.57 g).
^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 5.05 (s, 2H), 6.75 (s, 1H), 6.8 (s, 1H), 7.05 (d, 2H), 7.25 (s, 1H), 7.4 (m, 5H), 8.45 (s, 1H); *m/z* 410 $(M+H)^+$

3-({(1*S*)-1-[(Methyloxy)methyl]propyl}oxy)-5-[(phenylmethyl)oxy]benzoic acid



To a solution of methyl 3-({(1*S*)-1-[(methyloxy)methyl]propyl}oxy)-5-[(phenylmethyl)oxy]benzoate (6.85 g, 20 mmol) in 3:1 THF:methanol (100 mL) was added 1N lithium hydroxide solution in water (40 mL, 40 mmol), then a further 100 mL water was added portionwise at intervals while the resulting mixture was stirred for 2 hours. The organic solvents were removed by evaporation and the cloudy solution filtered. The pH of the filtrate was adjusted to 3 by the addition of 2 M hydrochloric acid. This was extracted with ethyl acetate (3 × 70 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the title compound as a colourless oil which solidified (6.36 g,).
^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 4.3 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.3-7.5 (m, 7H); *m/z* 329 $(M-H)^-$

Methyl 3-({(1*S*)-1-[(methyloxy)methyl]propyl}oxy)-5-[(phenylmethyl)oxy]benzoate

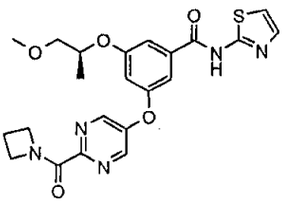


A stirred solution of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (7.5 g, 29 mmol), (*R*)-1-methoxy-butan-2-ol (3.76 g, 36.25 mmol) and triphenylphosphine (9.5 g, 36.25

mmol) in dry THF (75 mL) was cooled in an ice-bath and a solution of 40% DEAD in toluene (15.8 mL, 36.25 mmol) was added dropwise over 30 minutes. The reaction mixture was allowed to warm slowly to 10°C and stirred for 16 hours. The THF was evaporated and the residue was dissolved in 30% ethyl acetate in isohexane and cooled in ice. The resultant precipitate was removed by filtration and washed with 10% ethyl acetate in isohexane. The filtrate was evaporated and purified by column chromatography, eluting with 10% ethyl acetate in isohexane, to give the title compound as a colourless oil (6.85 g). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.35 (s, 3H), 3.55 (m, 2H), 3.9 (s, 3H), 4.3 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.25 (m, 2H), 7.4 (m, 5H); *m/z* 345 $(M+H)^+$

The preparation of (*R*)-1-methoxy-butan-2-ol was described in the literature [Coke, J. L.; Shue, R. S., *J. Org. Chem.* **38**, (1973), 2210-2211].
The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

Example 30: 3-{[2-(Azetidin-1-ylcarbonyl)pyrimidin-5-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide



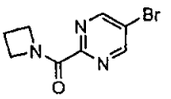
A mixture of 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide (130 mg, 0.42 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyrimidine (113 mg, 0.46 mmol), cesium carbonate (412 mg, 1.26 mmol) and bromotris(triphenylphosphine)copper(I) (118 mg, 0.13 mmol) in DMA (5 mL) was stirred in the a microwave reactor at 160°C for 4 hours. Ethyl acetate (50 mL) was added to the residue and the organics washed with water (20 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The residue was chromatographed on silica, eluting with a gradient of 0-10% methanol in ethyl acetate, to give the desired compound (67 mg). ^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.38 (quintet, 2H),

3.40 (s, 3H), 3.49 - 3.61 (m, 2H), 4.29 (t, 2H), 4.59 - 4.67 (m, 3H), 6.92 (t, 1H), 6.98 (d, 1H), 7.23 (d, 1H), 7.44 (t, 1H), 7.49 (t, 1H), 8.54 (s, 2H), 11.96 (s, 1H); *m/z* 470 $(M+H)^+$

The preparation of 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-1,3-thiazol-2-ylbenzamide was described earlier.

The preparation of 2-(azetidin-1-ylcarbonyl)-5-bromopyrimidine is described below:

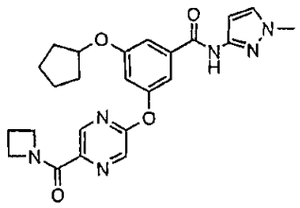
2-(Azetidin-1-ylcarbonyl)-5-bromopyrimidine



Oxalyl chloride (1.50 mL, 16.79 mmol), followed by DMF (2 drops), were added to a mixture of 5-bromopyrimidine-2-carboxylic acid (2.86 g, 14.0 mmol) in DCM (40 mL). The reaction was stirred at RT for 2 hours, the volatiles removed *in vacuo* and the residue dissolved in DCM (40 mL). Azetidine hydrochloride (1.44 g, 15.39 mmol), followed by triethylamine (4.29 mL, 30.78 mmol), were added and the mixture stirred at RT for 72 hours. The mixture was concentrated *in vacuo* and ethyl acetate (100 mL) added to the residue. The organics were washed with water (100 mL), citric acid (50 mL), saturated sodium bicarbonate solution (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow solid. The solid was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound as a yellow solid (0.86 g).

The preparation of 5-bromopyrimidine-2-carboxylic acid is described in the literature (International Patent Application WO 2005/028452).

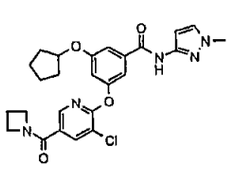
Example 31: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-(cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-(Cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (200 mg, 0.67 mmol), 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (159 mg, 0.80 mmol) and potassium carbonate (184 mg, 1.33 mmol) were dissolved / suspended in acetonitrile (3.5 mL). The reaction mixture was heated for 4 hours at 120°C in a microwave reactor. The mixture was cooled, filtered and concentrated *in vacuo*. The crude product was chromatographed on silica, eluting with 0-5% methanol in DCM, to give the required product as a white foam (282 mg).

^{1}H NMR δ (d_6-DMSO): 1.61 (m, 2H), 1.74 (m, 4H), 1.94 (m, 2H), 2.30 (m, 2H), 3.78 (s, 3H), 4.10 (t, 2H), 4.57 (t, 2H), 4.94 (m, 1H), 6.57 (d, 1H), 7.01 (t, 1H), 7.42 (m, 1H), 7.47 (m, 1H), 7.60 (d, 1H), 8.55 (d, 1H), 8.68 (d, 1H), 10.80 (s, 1H). *m/z* 463 $(M+H)^+$

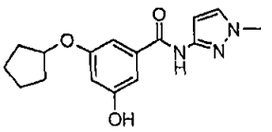
The following compound was made in an analogus fashion from 3-(cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine.

Example	Structure	m/z	^{1}H NMR (d_6-DMSO)
31a		496 $(M+H)^+$	δ: 1.69 (m, 2H), 1.82 (m, 4H), 2.03 (m, 2H), 2.34 (m, 2H), 3.99 (s, 3H), 4.14 (t, 2H), 4.45 (t, 2H), 5.03 (m, 1H), 6.65 (d, 1H), 7.06 (t, 1H), 7.47 (t, 1H), 7.54 (t, 1H), 7.68 (d, 1H), 8.30 (d, 1H), 8.42 (d, 1H), 10.87 (s, 1H).

The preparations of 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine were described earlier.

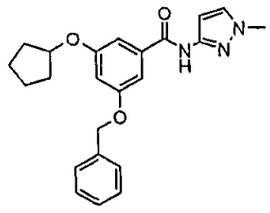
The preparation of 3-(cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide is described below:

3-(Cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



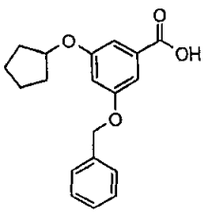
3-(Cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (1.87g, 4.78 mmol) was dissolved in ethanol (40 mL) and 10% palladium on charcoal (102 mg) catalyst added under argon. The reaction was stirred under an atmosphere of hydrogen for 86 hours, then filtered through Celite® and concentrated *in vacuo* to a light brown solid (1.31g). ^{1}H NMR δ (d_6-DMSO): 1.54 (m, 2H), 1.76 (m, 4H), 1.96 (m, 2H), 2.75 (s, 1H), 3.83 (s, 3H), 4.91 (m, 1H), 6.49 (m, 1H), 6.61 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 7.65 (s, 1H), 9.73 (br s, 1H); *m/z* 302 $(M+H)^+$

3-(Cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide



3-(Cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoic acid (3.14g, 10.0 mmol), 1-methyl-1H-pyrazol-3-amine (1.95g, 20 mmol) and HATU (4.95g, 13 mmol) were dissolved in DMF (12.5 mL) then DIPEA (3.49 mL, 20 mmol) was added. The resultant mixture was stirred at RT for 20 hours. The mixture was quenched with water (150 mL) and extracted with ethyl acetate (2 x 75 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to leave a yellow oil. The residue was chromatographed on silica, eluting with with 0-30% ethyl acetate in isohexane, to give the desired product as a clear gum (1.87g). ^{1}H NMR δ ($CDCl_3$): 1.59 (m, 4H), 1.83 (m, 4H), 3.79 (s, 3H), 4.76 (m, 1H), 5.08 (s, 2H), 6.66 (t, 1H), 6.82 (m, 1H), 7.01 (m, 1H), 7.08 (m, 1H), 7.26 (m, 1H), 7.33 (m, 1H), 7.35-7.45 (m, 4H), 8.67 (s, 1H); *m/z* 392 $(M+H)^+$

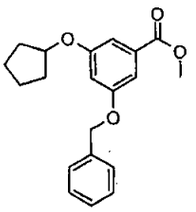
3-(Cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoic acid



Methyl 3-(cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoate (9.25g, 28.34 mmol) was dissolved in THF (120 mL) and a solution of lithium hydroxide mono hydrate (3.49 g, 85.0 mmol) in water (60 mL) added. The bi-phasic solution was stirred at RT for 16 hours (LCMS indicated reaction 80% complete), methanol (15 mL) added and the mixture stirred for a further 4 hours. The THF was removed *in vacuo* then water (40 mL) added and the pH adjusted to 7 with hydrochloric acid. The solid was collected and washed thoroughly with cold water (8.85 g).

^{1}H NMR δ (d_6-DMSO): 1.64 (m, 2H), 1.76 (m, 4H), 1.96 (m, 2H), 4.89 (m, 1H), 5.19 (s, 2H), 6.80 (s, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.34-7.53 (m, 5H); *m/z* 311 $(M+H)^+$

Methyl 3-(cyclopentyloxy)-5-[(phenylmethyl)oxy]benzoate

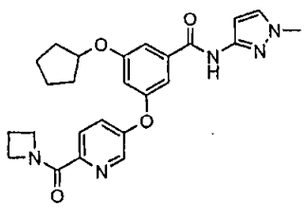


Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (10 g, 38.7 mmol), 1-cyclopentanol (6.135 mL, 58.07 mmol) and triphenylphosphine (15.24g, 58.07 mmol) were stirred under argon in THF (166 mL) and cooled in an ice bath to 5°C. DEAD (25.3 mL, 58.1 mmol) was added dropwise to the mixture, maintaining the internal temperature in the range 5 – 10°C. Stirring was continued for 16 hours. The mixture was concentrated *in vacuo*, re-dissolved in ethyl acetate (60 mL) and isohexane (60 mL), the resultant precipitate removed and the solution concentrated *in vacuo* to give a yellow oil. The residue was chromatographed on silica, eluting with 0-30% ethyl acetate in isohexane, to give a colourless oil which crystallised to a white solid under vacuum.

^{1}H NMR δ ($CDCl_3$): 1.62 (m, 2H), 1.71-1.98 (m, 6H), 3.90 (s, 3H), 4.76 (m, 1H), 5.08 (s, 2H), 6.69 (m, 1H), 7.16 (m, 1H), 7.23 (m, 1H), 7.29-7.44 (m, 5H); *m/z* 325 $(M+H)^+$

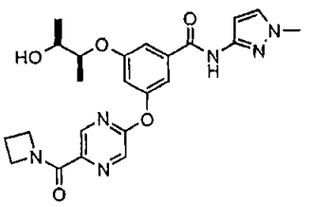
The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier.

Example 32: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-(cyclopentyloxy)-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



3-(Cyclopentyloxy)-5-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (200 mg, 0.67 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (193 mg, 0.80 mmol), bromotris(triphenylphosphine)copper (186 mg, 0.2 mmol) and caesium carbonate (230 mg, 0.70 mmol) were dissolved / suspended in DMA (3.5 mL). The reaction mixture was heated for 40mins at 200°C in a microwave reactor then allowed to cool, filtered and reduced *in vacuo*. The crude product was purified by chromatography on silica, eluting with 0-100% ethyl acetate in isohexane, to give the desired compound as a slightly yellow foam (176 mg). ^{1}H NMR δ (d_6-DMSO): 1.61 (m, 2H), 1.73 (m, 4H), 1.94 (m, 2H), 2.28 (m, 2H), 3.78 (s, 3H), 4.08 (t, 2H), 4.59 (t, 2H), 4.95 (m, 1H), 6.56 (d, 1H), 6.88 (t, 1H), 7.28 (m, 1H), 7.43 (t, 1H), 7.56 (m, 1H), 7.59 (d, 1H), 7.99 (d, 1H), 8.41 (m, 1H), 10.85 (s, 1H); m/z 462 $(M+H)^+$

Example 33: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1)



DIPEA (0.26 mL, 1.5 mmol) was added to a mixture of 5-[(3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid and 5-[(3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (1:1) (0.16 g, 0.37 mmol), azetidine hydrochloride (71 mg, 0.75 mmol) and HATU (299 mg, 0.79 mmol) in DMF (5 mL) and stirred at RT for 72 hours. Ethyl acetate (40 mL) was added and the mixture washed with water (2 x 30 mL), brine (30 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with 0-100% ethyl acetate in isohexane to give the titled mixture of diasteroisomers as a colourless oil. The mixture was separated by chiral preparatory HPLC on a Chiralpak IA (250 mm x 20 mm) EG014 column, eluting with 30% ethanol in tertbutylmethyl ether.

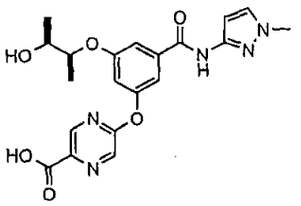
The first diastereomer eluted, **Example 33a**, was isolated as a white foam (18 mg). ^{1}H NMR δ ($CDCl_3$): 1.19 (d, 3H), 1.23 (d, 3H), 2.26 - 2.34 (m, 3H), 3.74 (s, 3H), 3.77 - 3.85 (m, 1H), 4.13 - 4.23 (m, 3H), 4.63 (t, 2H), 6.72 (d, 1H), 6.86 (t, 1H), 7.16 - 7.22 (m, 2H), 7.27 - 7.30 (m, 1H), 8.27 (d, 1H), 8.31 (s, 1H), 8.79 (d, 1H); *m/z* 467 $(M+H)^+$

The second diastereomer eluted, **Example 33b**, was isolated as a white foam (19 mg). ^{1}H NMR δ ($CDCl_3$): 1.19 (d, 3H), 1.22 (d, 3H), 2.27 - 2.36 (m, 3H), 3.73 (s, 3H), 3.76 - 3.84 (m, 1H), 4.13 - 4.22 (m, 3H), 4.62 (t, 2H), 6.72 (d, 1H), 6.86 (t, 1H), 7.17 - 7.19 (m, 1H), 7.21 (d, 1H), 7.28 (t, 1H), 8.26 (d, 1H), 8.40 (s, 1H), 8.79 (d, 1H); *m/z* 467 $(M+H)^+$

The preparation of a mixture of 5-[(3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid and 5-

[(3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (1:1) is described below:

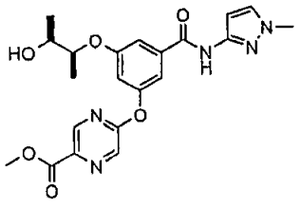
5-[(3-{[(1*R*,2*R*)-2-Hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid and 5-[(3-{[(1*S*,2*S*)-2-Hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylic acid (1:1)



Lithium hydroxide monohydrate (38 mg, 0.88 mmol) in water (3 mL) was added to methyl 5-[(3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate and methyl 5-[(3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate (1:1) (0.26 g, 0.59 mmol) in THF (6 mL) and the mixture stirred at RT for 72 hours. The THF was removed *in vacuo* and the aqueous residue adjusted to pH3 with citric acid, then extracted into ethyl actetate, washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the desired compound as a white solid (0.16 g).

^{1}H NMR δ (d_6-DMSO): 1.16 (d, 3H), 1.26 (d, 3H), 3.84 (s, 3H), 4.20 (m, 1H), 4.49 (m, 1H), 4.89 (d, 1H), 6.64 (d, 1H), 7.13 (t, 1H), 7.49 (s, 1H), 7.59 (s, 1H), 7.67 (d, 1H), 8.72 (d, 1H), 8.85 (d, 1H), 10.93 (s, 1H), 13.53 (s, 1H); *m/z* 426 $(M-H)^-$

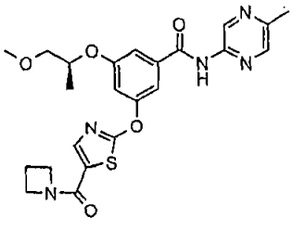
Methyl 5-[(3-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate and
Methyl 5-[(3-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-5-{[(1-methyl-1*H*-pyrazol-3-yl)amino]carbonyl}phenyl)oxy]pyrazine-2-carboxylate (1:1)



A mixture of 3-hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) (230 mg, 0.75 mmol), methyl 5-chloropyrazine-2-carboxylate (195 mg, 1.13 mmol) and potassium carbonate (208 mg, 1.51 mmol) in acetonitrile (5 mL) was stirred in a microwave reactor at 130°C for 3 hours. The solvent was removed *in vacuo* and water added. The mixture was acidified, extracted into ethyl acetate and the combined organics washed with brine, dried ($MgSO_4$), filtered and reduced *in vacuo* to give a yellow foam (265 mg), which was used in the next step without further purification. ^{1}H NMR δ ($CDCl_3$): 1.29 (m, 6H), 1.99 (s, 1H), 3.80 (s, 3H), 3.90 (quintet, 1H), 4.05 (s, 3H), 4.25 (quintet, 1H), 6.82 (d, 1H), 6.95 (t, 1H), 7.30 (m, 2H), 7.39 (s, 1H), 8.55 (s, 1H), 8.55 (s, 1H), 8.86 (s, 1H); *m/z* 442 $(M+H)^+$

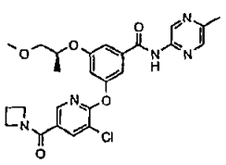
The preparation of 3-hydroxy-5-{[(1*R*,2*R*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and 3-hydroxy-5-{[(1*S*,2*S*)-2-hydroxy-1-methylpropyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide (1:1) was described earlier.

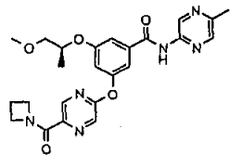
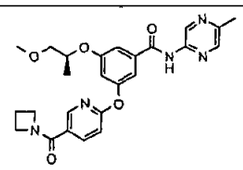
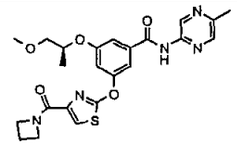
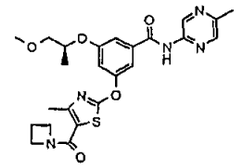
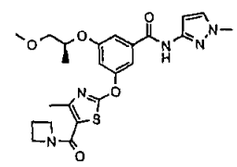
Example 34: 3-{[5-(Azetidin-1-ylcarbonyl)-1,3-thiazol-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide



Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide (159 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazole (152 mg, 0.75 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 120°C in a microwave reactor for 1 hour. The mixture was cooled to RT and ambient pressure, the acetonitrile evaporated *in vacuo*, the residue partitioned between water (25 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired product (181 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.35 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.1 – 4.4 (m, 4H), 4.55 (m, 1H), 7.0 (d, 1H),7.35 (d, 1H), 7.45 (s, 1H), 7.45 (s, 1H), 8.05 (s, 1H), 8.4 (s, 1H) and 9.45 (s, 1H). *m/z* 484 $(M+H)^+$.

The following compounds were synthesised in an analogous fashion from either 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide or 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide and the appropriate halogenated heterocycle:

Example	Structure	m/z	NMR
34a		512 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.1 – 4.35 (m, 4H), 4.55 (m, 1H), 6.9 (d, 1H), 7.2 (d, 1H), 7.35 (s, 1H), 8.05 (s, 1H), 8.1 (s, 1H), 8.2 (d, 1H), 8.3 (s, 1H) and 9.45 (s, 1H).

34b* **		479 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.2 (t, 2H), 4.55 (m, 1H), 4.65 (t, 2H), 6.9 (d, 1H),7.25 (d, 1H), 7.35 (d, 1H), 8.05 (s, 1H), 8.3 (s, 1H), 8.45 (s, 1H) 8.8 (s, 1H) and 9.45 (s, 1H).
34c		478 (M+H)	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.15 – 4.35 (m, 4H), 4.55 (m, 1H), 6.8 (d, 1H), 6.95 (d, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 8.0 (dd, 1H), 8.05 (s, 1H), 8.35 (d, 1H), 8.5 (s, 1H) and 9.5 (s, 1H).
34d		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.2 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.15 (t, 2H), 4.4 (t, 2H), 4.55 (m, 1H), 7.0 (d, 1H), 7.3 (d, 1H), 7.45 (s, 1H), 7.65 (s, 1H), 8.05 (s, 1H), 8.4 (s, 1H) and 9.45 (s, 1H).
34e		498 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.25 (m, 2H), 2.45 (s, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.1 – 4.2 (t, 4H), 4.55 (m, 1H), 7.0 (d, 1H), 7.35 (d, 2H), 8.05 (s, 1H), 8.4 (s, 1H) and 9.45 (s, 1H).
34f**		486 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.25 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4-3.55 (m, 2H), 3.7 (s, 3H), 4.1 – 4.2 (t, 4H), 4.5 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.2 (d, 1H), 7.3 (d, 2H) and 8.6 (s, 1H).

** The compound was partially crystallised from diethyl ether; mpt: melting onset 80.7°C.

*** **Example 34b**, 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide, was also prepared in the following manner.

A mixture of 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide (25.4 g, 80.0 mmol), 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (17.4 g, 88.0 mmol) and potassium carbonate (33.1 g, 240 mmol) in acetonitrile (254 mL) was heated at 60°C for 24 hours. The solvent was removed by evaporation and the residue

partitioned between ethyl acetate (15 vol) and water (10 vol). The layers were separated, the aqueous layer further extracted into ethyl acetate (2 x 10 vol) and the combined organics washed with water (2 x 5 vol), brine (5 vol), dried ($MgSO_4$), filtered, concentrated *in vacuo*. The residue was chromatographed on silica, eluting with ethyl acetate, to give the desired compound as a foam (33.7 g). The pure material was dissolved in hot *tert*-butylmethyl ether (30 vols), seeded with genuine crystalline sample (the seeds were isolated from a small scale crystallisation where material was dissolved in a minimum amount of hot *tert*-butylmethyl ether then isohexane added and the flask scratched to promote crystallisation) and stirred overnight. The mixture was cooled and the crystalline material (melting onset 110.3°C) collected by filtration (29.1 g).

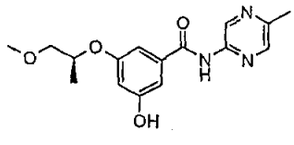
^{1}H NMR δ (d_6-DMSO): 1.27 (d, 3H), 2.30 (quin, 2H), 2.49 (s, 3H), 3.31 (s, 3H), 3.47 - 3.56 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.79 (td, 1H), 7.13 (t, 1H), 7.48 (td, 1H), 7.57 (td, 1H), 8.36 (d, 1H), 8.56 (d, 1H), 8.69 (d, 1H), 9.26 (d, 1H), 11.00 (s, 1H); *m/z* 479 $(M+H)^+$

This crystalline form could be converted to a different crystalline form by placeing approximately 30mg of material in a vial with a magnetic flea, and adding approximately 1 mL of water. A few (3) drops of methanol were added to this, and the vial was sealed with a lid. The slurry was then left to stir on a magnetic plate at RT (25°C). After 3 days, the sample was removed from the plate, the lid removed and the slurry left to dry under ambient conditions. The new crystalline form (melting onset 110.2°C) was shown to be different by XRPD analysis.

The title compound may also be crystallised by stirring a slurry of the compound in water.

The preparation of 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide is described below:

3-Hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide

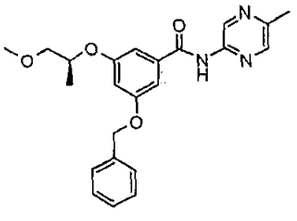


10% Palladium on charcoal (700 mg) was added to a solution of 3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide (7.0 g,

17.2 mmol) in ethanol (125 mL) and the mixture stirred at RT under a hydrogen atmosphere for 4 hours. The catalyst was removed by filtration and the ethanol evaporated *in vacuo*. The residue was crystallised from ethyl acetate to give the desired compound (4.22 g). ^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 – 3.5 (m, 2H), 4.5 (m, 1H), 6.3 (br, 1H), 6.55 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 8.05 (s, 1H), 8.45 (s, 1H) and 9.5 (s, 1H). *m/z* 318 $(M+H)^+$.

This reaction was also carried out using methanol as solvent and using 5 bar pressure of hydrogen.

3-{[(1*S*)-1-Methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide



Oxalyl chloride (2.1 mL, 24.0 mmol) was added to a solution of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (6.32 g, 20.0 mmol) in DCM (100 mL) and the mixture stirred at RT for 4 hours. The mixture was evaporated *in vacuo* to a residue, which was taken up in DCM (25 mL) and added to a stirred mixture of 2-amino-5-methylpyrazine (2.29 g, 21.0 mmol) and pyridine (1.94 mL, 24.0 mmol) in DCM (100 mL) at 5^0C - 10^0C. The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*. The residue was partitioned between water (50 mL) and ethyl acetate (150 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated to a residue, which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired compound (7.0 g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 – 3.5 (m, 2H), 4.5 (m, 1H), 5.0 (s, 2H), 6.7 (s, 1H), 7.0 (s, 1H), 7.05 (s, 1H), 7.35 (m, 5H), 8.05 (s, 1H), 8.3 (s, 1H) and 9.5 (s, 1H). *m/z* 408 $(M+H)^+$.

The preparation of 2-amino-5 methylpyrazine is described in the literature [*Tetrahedron Lett.* **2002**, 9287].

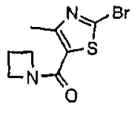
The preparation of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid was described earlier.

The preparation of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier.

The preparations of the halogenated heterocycles 5-(azetidin-1-ylcarbonyl)-2-chloro-1,3-thiazole, 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine, 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine, 5-(azetidin-1-ylcarbonyl)-2-chloropyridine and 4-(azetidin-1-ylcarbonyl)-2-bromo-1,3-thiazole were described earlier.

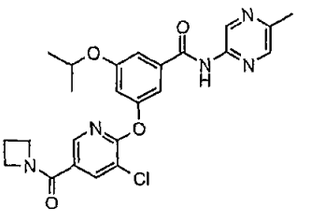
The preparation of 5-(azetidin-1-ylcarbonyl)-2-bromo-4-methyl-1,3-thiazole, used in **Examples 34e-f**, is described below:

5-(Azetidin-1-ylcarbonyl)-2-bromo-4-methyl-1,3-thiazole



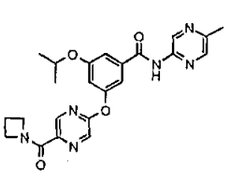
Oxalyl chloride (0.47 mL; 5.41 mmol) was added to a solution of 2-bromo-4-methyl-1,3-thiazole-5-carboxylic acid (1.0 g; 4.5 mmol) in DCM (25 mL). The mixture was stirred at RT for 18 hours, the DCM was evaporated *in vacuo*, the residue azeotroped with toluene (2 x 5 mL) and added to a solution of azetidine hydrochloride (503 mg; 5.41 mmol) and triethylamine (2.3 mL; 16.2 mmol) in DCM (50 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*, and the residue partitioned between water (75 mL) and ethyl acetate (150 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 40% ethyl acetate in isohexane, to give a solid which was crystallised from ethyl acetate / isohexane to give the desired compound (490 mg). ^1H NMR δ ($CDCl_3$): 2.35 (m, 2H), 2.55 (s, 3H) and 4.1 (t, 4H).

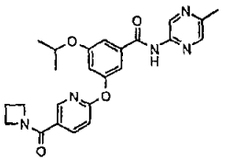
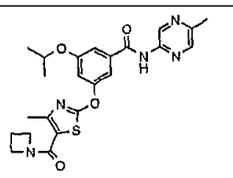
Example 35: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (144 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (173 mg, 0.75 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 120°C in a microwave reactor for 1 hour. The mixture was cooled to RT and ambient pressure, the acetonitrile evaporated *in vacuo*, the residue partitioned between water (25 mL) and ethyl acetate (50 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 75% ethyl acetate in isohexane, to give the desired compound (167 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.3 (m, 2H), 2.5 (s, 3H), 4.1 – 4.3 (m, 4H), 4.55 (m, 1H), 6.85 (d, 1H), 7.2 (d, 1H), 7.3 (s, 1H), 8.05 (s, 1H), 8.1 (s, 1H), 8.2 (s, 1H) 8.3 (s, 1H) and 9.45 (s, 1H). *m/z* 482 $(M+H)^+$.

The following compounds were prepared in an analogues fashion from 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide and the appropriate halogenated heterocycle:

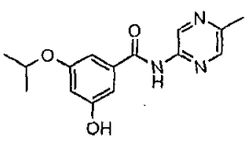
Example	Structure	m/z	NMR
35a		449 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.3 (m, 2H), 2.5 (s, 3H), 4.2 (t, 4H), 4.55 (m, 1H), 4.6 (t, 2H), 6.8 (d, 1H),7.2 (s, 1H), 7.35 (s, 1H), 8.05 (s, 1H), 8.25 (s, 1H), 8.35 (s, 1H), 8.8 (s, 1H) and 9.45 (s, 1H).

35b		448 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.3 (m, 2H), 2.5 (s, 3H), 4.15 (t, 2H), 4.3 (t, 2H), 4.55 (m, 1H), 6.8 (d, 1H), 6.95 (d, 1H), 7.2 (d, 1H), 7.25 (d, 1H), 8.0 (dd, 1H), 8.1 (s, 1H), 8.35 (s, 1H) 8.4 (s, 1H) and 9.45 (s, 1H).
35c*		468 $(M+H)^+$	^{1}H NMR δ (DMSO d_6): 1.3 (d, 6H), 2.25 (m, 2H), 2.45 (s, 3H), 3.3 (s, 3H), 4.0 – 4.2 (br, 4H), 4.8 (m, 1H),7.2 (d, 1H), 7.6 (d, 2H), 8.35 (s, 1H), 9.25 (s, 1H) and 11.0 (s, 1H).

* Compound was crystallised from ethyl acetate and isohexane; mpt: melting onset 140.4°C.

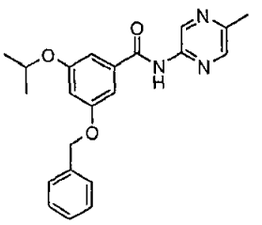
The preparation of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide is described below:

3-Hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



10% Palladium on charcoal (550 mg) was added to a solution of 3-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide (5.5 g, 14.6 mmol) in ethanol (75 mL) and THF (50 mL) and the mixture stirred at RT under a hydrogen atmosphere for 24 hours. The catalyst was removed by filtration and the filtrates evaporated *in vacuo* to a residue which was crystallised from ethyl acetate to give the desired compound (3.42g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.5 (s, 3H), 4.5 (m, 1H), 5.8 (br, 1H), 6.5 (d, 1H), 6.9 (d, 1H), 6.95 (d, 1H), 8.05 (s, 1H), 8.4 (s, 1H) and 9.5 (s, 1H). *m/z* 288 $(M+H)^+$.

3-[(1-Methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)-5-[(phenylmethyl)oxy]benzamide



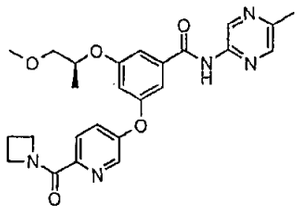
Oxalyl chloride (2.1 mL, 24.0 mmol) was added to a solution of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (5.72 g, 20.0 mmol) in DCM (100 mL) and the mixture stirred at ambient RT for 4 hours. The mixture was evaporated *in vacuo* to a residue, which was taken up in DCM (25 mL) and added to a stirred mixture of 2-amino-5-methylpyrazine (2.29 g, 21.0 mmol) and pyridine (1.94 mL, 24.0 mmol) in DCM (100 mL) at 5°C - 10°C. The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo* to a residue, which was partitioned between water (50 mL) and ethyl acetate (150 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 30% ethyl acetate in isohexane, and crystallised from ethyl acetate / isohexane to give the desired compound (5.52 g).

^1H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.5 (s, 3H), 4.5 (m, 1H), 5.0 (s, 2H), 6.6 (s, 1H), 6.95 (s, 1H), 7.0 (s, 1H), 7.35 (m, 5H), 8.05 (s, 1H), 8.3 (s, 1H) and 9.5 (s, 1H). *m/z* 378 $(M+H)^+$.

The preparations of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid and 2-amino-5-methylpyrazine were described earlier.

The preparations of the halogenated heterocycles 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine, 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine, 5-(azetidin-1-ylcarbonyl)-2-chloropyridine and 5-(azetidin-1-ylcarbonyl)-2-bromo-4-methyl-1,3-thiazole were described earlier.

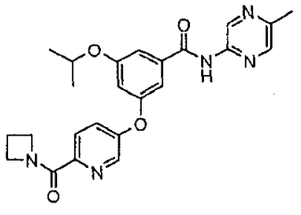
Example 36: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide



Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide (159 mg, 0.5 mmol) and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (181 mg, 0.75 mmol) and bromotris(triphenylphosphine)copper (93 mg, 0.1 mmol) in DMA (5 mL) and the stirred mixture heated at 160°C in a microwave reactor for 4 hours. The mixture was cooled to RT and ambient pressure, partitioned between water (75 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with ethyl acetate, to give the desired compound that was crystallised from ether (45 mg, melting onset 113.8°C). The compound may also be crystallised from ethyl acetate, giving rise to an alternative crystalline form (melting onset 132.7°C). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 – 3.55 (m, 2H), 4.2 (t, 2H), 4.55 (m, 1H), 4.65 (t, 2H), 6.75 (d, 1H), 7.05 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 8.0 (s, 1H), 8.05 (d, 1H), 8.25 (d, 1H), 8.3 (s, 1H) and 9.45 (s, 1H). *m/z* 478 $(M+H)^+$.

The preparations of 2-(azetidin-1-ylcarbonyl)-5-bromopyridine and 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide were described earlier.

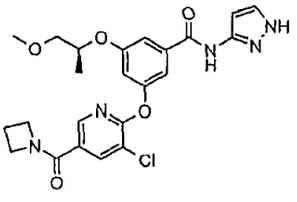
Example 37: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxyl-*N*-(5-methylpyrazin-2-yl)benzamide



Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (144 mg, 0.5 mmol) and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (181 mg, 0.75 mmol) and bromotris(triphenylphosphine)copper (93 mg, 0.1 mmol) in DMA (5 mL) and the stirred mixture heated at 160°C in a microwave reactor for 4 hours. The mixture was cooled to RT and ambient pressure, partitioned between water (75 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with 75% ethyl acetate in isohexane, to give the desired compound (crystallised from ether) (72 mg). ^1H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.3 (m, 2H), 2.5 (s, 3H), 4.2 (t, 2H), 4.5 (m, 1H), 4.65 (t, 2H), 6.7 (s, 1H), 7.05 (s, 1H), 7.2 (s, 1H), 7.3 (d, 1H), 8.0 (br, 2H), 8.3 (br, 2H) and 9.45 (s, 1H). *m/z* 448 $(M+H)^+$. Mpt (melting onset) 125.7°C.

The preparations of 2-(azetidin-1-ylcarbonyl)-5-bromopyridine and 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide were described earlier.

Example 38: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-1*H*-pyrazol-3-ylbenzamide



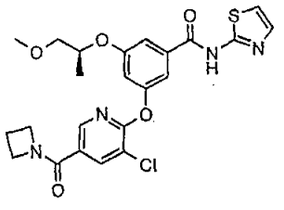
A mixture of 1,1-dimethylethyl 3-{[(3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)carbonyl]amino}-1*H*-pyrazole-1-carboxylate (196 mg, 0.5

mmol), 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (128 mg, 0.55 mmol) and potassium carbonate (138 mg, 1.0 mmol) in acetonitrile (5 mL) was stirred in a microwave reactor at 120°C for 4 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil which was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound as a white foam (142 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.31 (quin, 2H), 3.33 (s, 3H), 3.43 - 3.53 (m, 2H), 4.11 - 4.33 (m, 4H), 4.54 (q, 1H), 6.78 (s, 1H), 6.86 (s, 1H), 7.24 (s, 1H), 7.33 (s, 1H), 7.42 (s, 1H), 8.06 (d, 1H), 8.12 (s, 1H), 9.98 (s, 1H); *m/z* 486 $(M+H)^+$

The preparations of 1,1-dimethylethyl 3-{[(3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}phenyl)carbonyl]amino}-1*H*-pyrazole-1-carboxylate and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine were described earlier.

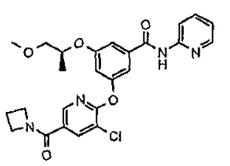
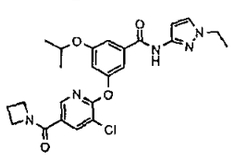
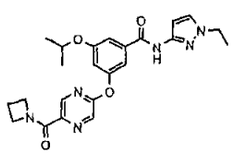
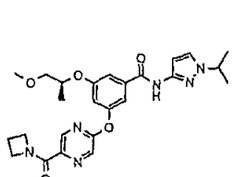
Example 39: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-1,3-thiazol-2-ylbenzamide

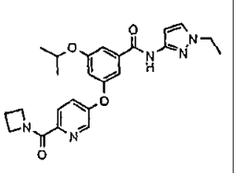
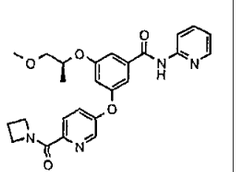
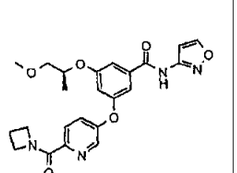
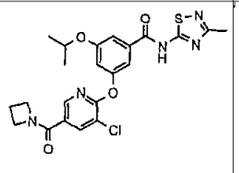
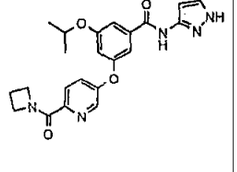
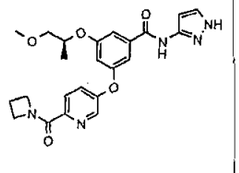


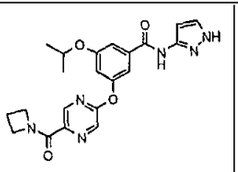
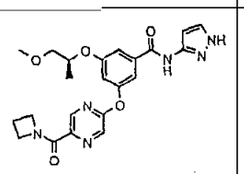
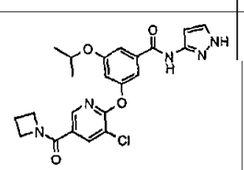
DIPEA (0.129 mL) was added to a suspension of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid (168 mg), HATU (190 mg) and 2-aminothiazole (40 mg) in DMF (2 mL) and the mixture stirred at RT for 16 hours. Water (30 mL) was added and the mixture extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to a residue which was chromatographed on silica, eluting with 50-100% ethyl acetate in isohexane, to give the desired compound (75 mg).

^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.31 (quin, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 4.12 - 4.33 (m, 4H), 4.55 (q, 1H), 6.91 (d, 1H), 6.95 (s, 1H), 7.30 (s, 1H), 7.31 (d, 1H), 7.40 (s, 1H), 8.08 (s, 1H), 8.16 (s, 1H); *m/z* 503 $(M+H)^+$

The following compounds were made in an analogous fashion from either 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid, 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid, 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid, 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid, 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid or 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid and the appropriate aminoheterocycle.

Example	Structure	m/z	NMR
39a		497 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.32 (quin, 2H), 3.34 (s, 3H), 3.41 - 3.56 (m, 2H), 4.11 - 4.34 (m, 4H), 4.55 (q, 1H), 6.90 (s, 1H), 7.00 (t, 1H), 7.22 (s, 1H), 7.34 (s, 1H), 7.68 (t, 1H), 8.08 (s, 1H), 8.19 (s, 1H), 8.23 (s, 1H), 8.27 (d, 1H), 8.37 - 8.56 (m, 1H)
39b		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 6H), 1.39 (t, 3H), 2.31 (quin, 2H), 4.00 (q, 2H), 4.11 - 4.34 (m, 4H), 4.54 (quin, 1H), 6.73 (s, 1H), 6.81 (s, 1H), 7.14 (s, 1H), 7.24 (s, 2H), 8.09 (s, 1H), 8.18 (s, 1H), 8.39 (s, 1H)
39c		451 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 6H), 1.39 (t, 3H), 2.31 (quin, 2H), 3.99 (q, 2H), 4.19 (t, 2H), 4.53 (quin, 1H), 4.61 (t, 2H), 6.72 (s, 1H), 6.80 (s, 1H), 7.14 (s, 1H), 7.25 (s, 2H), 8.25 (s, 1H), 8.36 (s, 1H), 8.79 (s, 1H)
39d		495 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 1.41 (d, 6H), 2.31 (quin, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 4.19 (t, 2H), 4.30 (quin, 1H), 4.54 (q, 1H), 4.62 (t, 2H), 6.71 (s, 1H), 6.86 (s, 1H), 7.18 (s, 1H), 7.28 (s, 1H), 7.30 (s, 1H), 8.25 (s, 1H), 8.33 (s, 1H), 8.79 (s, 1H)

39e		450 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 1.39 (t, 3H), 2.28 (quin, 2H), 4.00 (q, 2H), 4.18 (t, 2H), 4.52 (quin, 1H), 4.64 (t, 2H), 6.65 (s, 1H), 6.71 (s, 1H), 7.00 (s, 1H), 7.16 (s, 1H), 7.25 (s, 1H), 7.30 (d, 1H), 8.04 (d, 1H), 8.25 (s, 1H), 8.32 (s, 1H)
39f		463 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.28 (quin, 2H), 3.34 (s, 3H), 3.43 - 3.54 (m, 2H), 4.18 (t, 2H), 4.56 (q, 1H), 4.64 (t, 2H), 6.76 (s, 1H), 7.03 (q, 1H), 7.10 (s, 1H), 7.27 (s, 1H), 7.31 (d, 1H), 7.71 (t, 1H), 8.05 (d, 1H), 8.23 (s, 1H), 8.26 (s, 1H), 8.29 (d, 1H), 8.59 (s, 1H)
39g		453 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.27 (quin, 2H), 3.32 (s, 3H), 3.41 - 3.53 (m, 2H), 4.17 (t, 2H), 4.54 (q, 1H), 4.63 (t, 2H), 6.78 (s, 1H), 7.11 (s, 1H), 7.15 (s, 1H), 7.27 (s, 1H), 7.29 (d, 1H), 8.03 (d, 1H), 8.18 (s, 1H), 8.25 (s, 1H), 9.43 (s, 1H)
39h		488 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.22 (d, 6H), 2.16 (quin, 2H), 2.41 (s, 3H), 3.95 (t, 2H), 4.26 (t, 2H), 4.67 (quin, 1H), 7.05 (s, 1H), 7.43 (s, 1H), 7.52 (s, 1H), 8.15 (s, 1H), 8.25 (s, 1H), 13.32 (s, 1H)
39i*		422 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.27 (quin, 2H), 4.16 (t, 2H), 4.51 (quin, 1H), 4.62 (t, 2H), 6.68 (s, 1H), 6.72 (s, 1H), 7.08 (s, 1H), 7.23 (s, 1H), 7.28 (d, 1H), 7.46 (s, 1H), 7.99 (d, 1H), 8.24 (s, 1H), 9.25 (s, 1H)
39j*+		452 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.28 (quin, 2H), 3.33 (s, 3H), 3.42 - 3.55 (m, 2H), 4.16 (t, 2H), 4.54 (q, 1H), 4.62 (t, 2H), 6.73 (s, 1H), 6.75 (s, 1H), 7.12 (s, 1H), 7.28 (d, 1H), 7.32 (s, 1H), 7.43 (s, 1H), 8.00 (d, 1H), 8.24 (s, 1H), 9.78 (s, 1H)

39k*++		423 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.31 (quin, 2H), 4.19 (t, 2H), 4.52 (quin, 1H), 4.61 (t, 2H), 6.76 - 6.78 (m, 2H), 7.19 (s, 1H), 7.27 (s, 1H), 7.37 (s, 1H), 8.29 (s, 1H), 8.74 (s, 1H), 10.03 (s, 1H)
39l*		453 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.31 (quin, 2H), 3.33 (s, 3H), 3.42 - 3.54 (m, 2H), 4.18 (t, 2H), 4.53 (q, 1H), 4.61 (t, 2H), 6.78 (s, 1H), 6.83 (s, 1H), 7.22 (s, 1H), 7.35 (s, 2H), 8.31 (s, 1H), 8.73 (s, 1H), 10.38 (s, 1H)
39m*		456 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.31 (quin, 2H), 4.15 (t, 2H), 4.25 (t, 2H), 4.53 (quin, 1H), 6.79 (s, 2H), 7.20 (s, 1H), 7.26 (s, 1H), 7.33 (s, 1H), 8.08 (s, 1H), 8.10 (s, 1H), 10.44 (s, 1H)

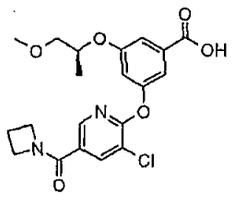
* The reactions were carried out using 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate as the amino heterocycle, the resultant products were dissolved in acetonitrile (4 mL) and ethanol (0.5 mL) and heated in a microwave reactor at 150°C for 12 minutes. The mixtures were allowed to cool then concentrated *in vacuo* to give the desired products.

+ This compound was crystallised from ethyl acetate and isohexane using vapour diffusion techniques.

++ This compound was crystallised from acetonitrile, melting point (melting onset) 108.5 °C.

The preparation of 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate was described earlier. The preparation of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid is given below:

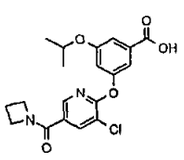
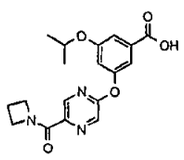
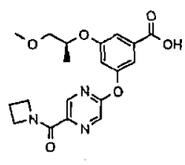
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid



A mixture of methyl 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate (240 mg, 0.1 mmol), 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (278 mg, 1.2 mmol) and potassium carbonate (276 mg, 2.0 mmol) in DMA (5 mL) was stirred at 120°C for 16 hours. The solution was poured into water (30 mL) and acidified with 1N hydrochloric acid before being extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoate (as evidenced by LCMS data only *m/z* 435 $(M+H)^+$) as a brownish oil (550 mg). The crude methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoate (434 mg,1 mmol) was dissolved in THF (15 mL) and methanol (5 mL) then 1N aqueous Lithium hydroxide solution (2 mL) added followed by the dropwise addition of water until a clear solution obtained. The mixture was stirred was stirred for 4 hours at RT and the organics removed by evaporation. The aqueous solution was filtered, extracted with ethyl acetate (10 mL) and the aqueous layer acidified with 2N hydrochloric acid. The acidified layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts washed with water (10 mL), brine (10 mL) and concentrated *in vacuo* to give the desired compound as a pale oil (375 mg). ^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.32 (quin, 2H), 3.34 (s, 3H), 3.42 - 3.55 (m, 2H), 4.13 - 4.34 (m, 4H), 4.54 (q, 1H), 6.93 (s, 1H), 7.40 (s, 1H), 7.48 (s, 1H), 8.08 (s, 1H), 8.19 (s, 1H), *m/z* 421 $(M+H)^+$

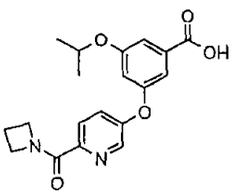
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid, 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid and 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid were made in an analogous fashion from either methyl

3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate or methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate and the appropriate halogenated heterocycle.

Structure	m/z	NMR
	391 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 6H), 2.31 (quin, 2H), 4.11 - 4.35 (m, 4H), 4.53 (quin, 1H), 6.87 (s, 1H), 7.37 (s, 1H), 7.42 (s, 1H), 8.09 (s, 1H), 8.19 (s, 1H)
	358 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.28 (6H, d), 2.26 - 2.34 (2H, quin), 4.10 (2H, t), 4.56 (2H, t), 4.65 - 4.71 (1H, quin), 7.11 (1H, t), 7.29 (1H, s), 7.33 (1H, s), 8.53 (1H, s), 8.66 (1H, s)
	388 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.31 (quin, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 4.20 (t, 2H), 4.50 - 4.57 (m, 1H), 4.62 (t, 2H), 6.92 (t, 1H), 7.39 (s, 1H), 7.49 (s, 1H), 8.25 (s, 1H), 8.78 (s, 1H)

The preparation of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid is described below:

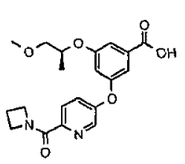
3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid



A mixture of methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate (0.84 g, 4 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (1.16 g, 4.8 mmol), cesium carbonate (3.92 g, 1.2 mmol) and bromotris(triphenylphosphine)copper(I) (744 mg, 0.8 mmol) in DMA (20 mL) was stirred in a microwave reactor at 160°C for 6 hours. The mixture was diluted with water (100 mL), washed with ethyl actate (2 x 20 mL) and the aqueous layer filtered then

acidified with 2N hydrochloric acid. The acidic layer was extracted with ethyl acetate (3 x 50 mL), the combined organics washed with water (2 x 20 mL), brine (20 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was triturated with ether to give the desired compound as a white solid (1.06 g). ^{1}H NMR δ (d_6-DMSO): 1.28 (d, 6H), 2.28 (quin, 2H), 4.08 (t, 2H), 4.59 (t, 2H), 4.69 (quin, 1H), 6.98 (t, 1H), 7.10 (s, 1H), 7.28 (s, 1H), 7.56 (d, 1H), 7.99 (d, 1H), 8.41 (s, 1H); *m/z* 357 $(M+H)^+$

3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid was prepeared in an analogous fashion from 2-(azetidin-1-ylcarbonyl)-5-bromopyridine and methyl 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate.

Structure	m/z	NMR
	387 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.28 (quin, 2H), 3.33 (s, 3H), 3.40 - 3.54 (m, 2H), 4.20 (t, 2H), 4.53 (quin, 1H), 4.64 (t, 2H), 6.79 (t, 1H), 7.25 (s, 1H), 7.42 (s, 1H), 7.99 - 8.11 (m, 1H), 8.19 - 8.35 (m, 1H)

The preparations of methyl 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]benzoate, methyl 3-hydroxy-5-[(1-methylethyl)oxy]benzoate and the appropriate halogenated heterocycles were described earlier.

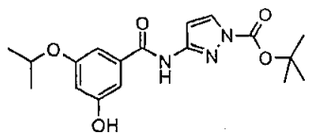
3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]-*N*-1*H*-pyrazol-3-ylbenzamide, **Example 39k**, was also prepared in the following manner from 1,1-dimethylethyl 3-[({3-hydroxy-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate.

1,1-Dimethylethyl 3-[({3-hydroxy-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate (56.3 g, 0.16 mol) was dissolved in acetonitrile (500 mL) and charged to a 3L fixed vessel. Potassium carbonate – 325 mesh - (64.5 g, 0.47 mol) was added, followed by 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (33.5 g, 0.17 mol) with a 100 mL acetonitrile charge wash. The mixture was stirred rapidly and warmed to 60°C under nitrogen. Additional acetonitrile (250 mL) was added followed, after 1.5 hours, by

the addition of DMF (150 mL) to dissolve residual solid material. The reaction was stirred overnight then allowed to cool to RT and filtered. The filtrate was concentrated under vacuum to remove the acetonitrile and the residual solution poured into water (1500 mL) with stirring. The precipitated solid was filtered, dissolved in DCM (560 mL), washed with 1:1 brine / saturated aqueous solution of sodium hydrogen carbonate (2 x 500 mL) and dried ($MgSO_4$). The organic solution was filtered and TFA (50 mL). The solution was stirred at RT for 3 hours. Additional TFA (50 mL) was added and the mixture stirred at 30°C for a further 3 hours then at RT overnight. The solvent was removed under vacuum and the residue azeotroped with toluene. The orange oily residue was dissolved in ethyl acetate (500 mL) and washed with a saturated solution of sodium hydrogen carbonate (2 x 500 mL), brine (500 mL), dried ($MgSO_4$) and concentrated to leave a pale yellow waxy solid (64 g). The solid was triturated with ethyl acetate (200 mL) at 45°C for 2 hours, filtered, washed with ethyl acetate and dried in a vacuum oven at 40°C overnight to leave a white solid (52 g). The crude solid was columned on silica, eluting with a mixture of a 7N ammonia in methanol solution in DCM (0.5 - 6.5% methanol gradient), to give pure desired material [pure 1] (23.6 g, 99.1% pure by HPLC) and less pure material recovered from mixed fractions and previous liquors (34.5 g, 82.8% pure by HPLC). The impure material was dissolved in DCM (50 mL) and a white solid crystallised out. The solid was removed by filtration and washed with DCM to give pure desired material [pure 2] (6.5 g, 98.3% pure by HPLC). The filtrate was columned on silica, eluting with 7N ammonia in methanol solution in DCM (0 - 5% methanol gradient), to give the desired material [pure 3] (18.3 g, 98.7% pure by HPLC). Pures 1, 2 & 3 were combined (48.4 g) and charged to a 3L fixed vessel. Ethyl acetate (500 mL, 10 vol) was added and the mixture was heated to reflux with stirring, additional ethyl acetate (400 mL, 8 vol) was added and the remaining solid material removed by hot filtration. The filtrate was cooled to 60°C and isohexane (250 mL) added dropwise. The slurry was cooled to 20°C over approx 1 hour and then stirred at RT overnight. The slurry was filtered and the solid washed with isohexane (2 x 200 mL) then dried in a vacuum oven at 40°C to leave a white solid (34.5 g). This solid was further dried in a vacuum oven at 60°C overnight to leave the desired compound as a white powder (33.1 g). This is a different crystal form to that previously described, melting point (melting onset) 113.8°C.

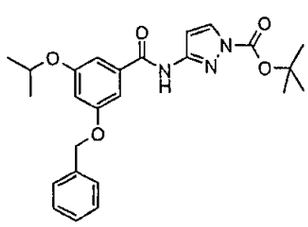
The preparation of 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine was described earlier.
The preparation of 1,1-dimethylethyl 3-[({3-hydroxy-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate is described below.

1,1-Dimethylethyl 3-[({3-hydroxy-5-[(1-methylethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate



1,1-Dimethylethyl 3-[({3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate (76.4 g, 0.17 mol) was dissolved in ethanol (750 mL, 10 vol) and 10% palladium on charcoal (water wet) (7.5 g) added. The mixture was hydrogenated for 18 hours at 25°C and a pressure of 5 bar. The catalyst was removed by filtration through celite ® and the cake washed with methanol (250 mL). The combined filtrate was concentrated under vacuum to leave a beige foamy solid which was chromatographed on silica, eluting with 10-70% ethyl acetate in isohexane, to give the desired material as a white foam solid (56.4 g). ^{1}H NMR δ ($CDCl_3$): 1.30 (d, 6H), 1.64 (s, 9H), 4.49 - 4.55 (m, 1H), 6.67 (t, 1H), 6.98 (d, 2H), 7.10 (d, 1H), 8.02 (d, 1H), 9.21 (s, 1H); *m/z* 360 $(M-H)^-$

1,1-Dimethylethyl 3-[({3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]phenyl}carbonyl)amino]-1*H*-pyrazole-1-carboxylate

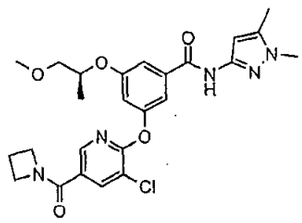


A solution of oxalyl chloride (76 mL, 0.87 mol) in DCM (125 mL) was added dropwise to a slurry of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid (50 g, 0.17 mol) and DMF (1 mL) in DCM (300 mL). The reaction was stirred at RT for 2 hours then the solvent removed under vacuum and the residue azeotroped with toluene (200 mL). The

oily residue was dissolved in dry pyridine (100 mL) and the mixture added, over 5 minutes, to a solution of 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate (38.4 g, 0.21 mol) in dry pyridine (325 mL) under nitrogen. The reaction was stirred at RT for 1 hour, the solvent removed under vacuum and the residue azeotroped with toluene. The residue was partitioned between DCM (500 mL) and water (500 mL) and the organic layer washed with a saturated aqueous solution of sodium hydrogen carbonate (500 mL), brine (500 mL) and dried ($MgSO_4$). The organic solution was concentrated under vacuum and the residue twice azeotroped with toluene to leave an orange resin (88.8 g). The resin was chromatographed on silica, eluting with 25-50% ethyl acetate in isohexane, to give the desired material as a pale yellow foam (76.4 g). ^{1}H NMR δ ($CDCl_3$): 1.33 (d, 6H), 1.56 (s, 9H), 4.49 - 4.55 (m, 1H), 5.04 (s, 2H), 6.69 (t, 1H), 7.00 (t, 1H), 7.06 - 7.07 (m, 1H), 7.17 (d, 1H), 7.32 - 7.45 (m, 5H), 8.04 (d, 1H), 9.48 (s, 1H); *m/z* 450 $(M-H)^-$

The preparations of 3-[(1-methylethyl)oxy]-5-[(phenylmethyl)oxy]benzoic acid and 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate were described earlier.

Example 40: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-*N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide

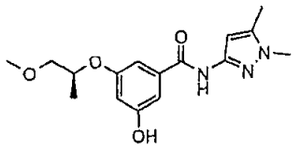


A solution of *N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide (0.62 mmol) in acetonitrile (5 mL), was treated with potassium carbonate (1.24 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (0.68 mmol), before being heated to 120°C in a microwave reactor for 4.5 hours. The mixture was evaporated *in vacuo*, before being partitioned between DCM (20 mL) and water (20 mL). The organics were evaporated *in vacuo* then chromatographed on silica, eluting with 0-10% methanol in ethyl acetate, to give the desired compound as a white foam (160 mg).

^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 2.24 (s, 3H), 2.26 (m, 2H), 3.30 (s, 3H), 3.50 (m, 2H), 3.66 (s, 3H), 4.05 (t, 2H), 4.37 (t, 2H), 4.78 (m, 1H), 6.42 (s, 1H), 7.03 (t, 1H), 7.38 (t, 1H), 7.51 (t, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 10.76 (s, 1H); *m/z* 514,516 $(M+H)^+$

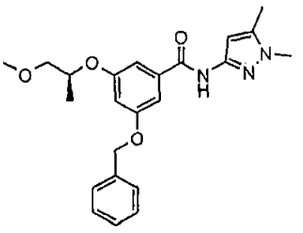
The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine was described earlier. The preparation of *N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide is described below:

N-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide



A solution of *N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-[(phenylmethyl)oxy]benzamide (2.57 mmol) in ethanol (40 mL), under argon was treated with 10% palladium on carbon (100 mg, wetted with 0.1 mL water and 1 mL ethanol). The flask was evacuated and filled with hydrogen, this procedure was repeated 4 times. The mixture was left to stir at RT overnight under an atmosphere of hydrogen then the reaction filtered through celite® and the cake washed with ethanol (50 mL) and ethyl acetate (50 mL). The combined organic layers were evaporated *in vacuo* to give the desired compound as a white foam (597 mg). ^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.25 (s, 3H), 3.31 (s, 3H), 3.47 (m, 2H), 3.66 (s, 3H), 4.66 (m, 1H), 6.40 (s, 1H), 6.46 (t, 1H), 6.95 (t, 1H), 7.06 (t, 1H), 9.60 (s, 1H), 10.49 (s, 1H); *m/z* 320 $(M+H)^+$

N-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-5-[(phenylmethyl)oxy]benzamide



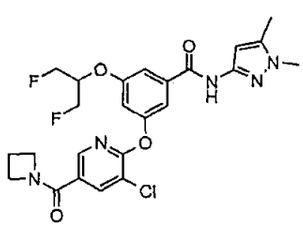
A solution of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid (4.11 mmol) in DMF (10 mL) was treated with the 1,5-dimethyl-1*H*-pyrazol-3-ylamine (4.52 mmol), DIPEA (5.93 mmol) and HATU (3.85 mmol) and stirred at RT overnight, under an argon atmosphere. The mixture was poured onto water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was washed with brine (20 mL) and evaporated *in vacuo* before chromatography on silica, eluting with 20-80% ethyl acetate in isohexane, to afford the desired compound as a yellow oil (1.05 g).

^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.25 (s, 3H), 3.30 (s, 3H), 3.48 (m, 2H), 3.67 (s, 3H), 4.71 (m, 1H), 5.16 (s, 2H), 6.42 (s, 1H), 6.73 (t, 1H), 7.20 (t, 1H), 7.26 (t, 1H), 7.34 (m, 1H), 7.41 (m, 2H), 7.46 (m, 2H), 10.62 (s, 1H); *m/z* 410 $(M+H)^+$

The preparation of 3-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-5-{[phenylmethyl]oxy}benzoic acid was described earlier.

The 1,5-dimethyl-1*H*-pyrazol-3-ylamine was prepared according to the literature route [*J. Het. Chem.*, (1982), *19*, 1267].

Example 41: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-*N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzamide



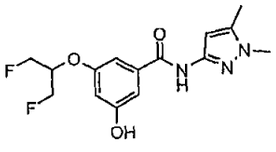
A solution of *N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzamide (0.61 mmol) in acetonitrile (5 mL), was treated with the potassium carbonate (1.23 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (0.68 mmol), before being heated to 120°C in a microwave reactor for 4 hours. The mixture was filtered and evaporated *in vacuo* before being chromatographed on silica, eluting with 0-5% methanol in ethyl acetate, to give the desired compound as a white foam (175 mg).

^{1}H NMR δ (d_6-DMSO): 2.27 (m, 5H), 3.66 (s, 3H), 4.06 (t, 2H), 4.37 (t, 2H), 4.65 (m, 1H), 4.73 (m, 1H), 4.77 (m, 1H), 4.85 (m, 1H), 5.10 (m, 1H), 6.42 (s, 1H), 7.16 (t, 1H), 7.45 (t, 1H), 7.60 (t, 1H), 8.23 (d, 1H), 8.35 (d, 1H), 10.71 (s, 1H) *m/z* 520 $(M+H)^+$

The preparation of 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine was described earlier.

The preparation of *N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzamide is described below:

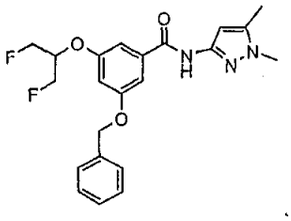
N-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzamide



A solution of *N*-(1,5-dimethyl-1*H*-pyrazol-3-yl)-3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzamide (1.89 mmol) in ethanol (30 mL) was treated with 10% palladium on carbon (78 mg, wetted with 1 mL ethanol). The flask was evacuated and filled with hydrogen and this procedure repeated a further 4 times. The mixture was left to stir at RT overnight under an atmosphere of hydrogen then the mixture filtered through celite® and the cake washed with ethanol (50 mL) and ethyl acetate (50 mL). The combined organics were evaporated *in vacuo* to give the desired compound as a white foam (613 mg).

^{1}H NMR δ (d_6-DMSO): 2.52 (s, 3H), 3.66 (s, 3H), 4.66 (m, 2H), 4.77 (m, 2H), 4.97 (m, 1H), 6.41 (s, 1H), 6.56 (t, 1H), 7.02 (m, 1H), 7.15 (t, 1H), 10.52 (s, 1H); *m/z* 326 $(M+H)^+$

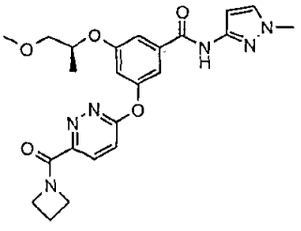
N-(1,5-Dimethyl-1*H*-pyrazol-3-yl)-3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzamide



A solution of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid (2.96 mmol) in DMF (5 mL) was treated with 1,5-dimethyl-1*H*-pyrazol-3-ylamine (3.11 mmol), DIPEA (5.93 mmol) and HATU (3.85 mmol) and stirred at RT overnight. The mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 75 mL). The organics were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* before chromatography on solica, eluting with 50-100% ethyl acetate in isohexane, to give the desired compound as a colourless glass (784 mg). ^{1}H NMR δ (d_6-DMSO): 2.81 (s, 3H), 3.67 (s, 3H), 4.66 (m, 2H), 4.78 (m, 2H), 5.04 (m, 1H), 5.69 (s, 2H), 6.43 (s, 1H), 6.85 (t, 1H), 7.28 (m, 1H), 7.32 (m, 1H), 7.35 (m, 1H), 7.41 (m, 2H), 7.47 (m, 2H), 10.64 (s, 1H); *m/z* 416 $(M+H)^+$

The preparations of 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoic acid and 1,5-dimethyl-1*H*-pyrazol-3-ylamine were described earlier.

Example 42: 3-{[6-(Azetidin-1-ylcarbonyl)pyridazin-3-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide



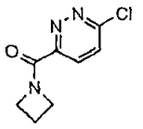
A mixture of 3-(azetidin-1-ylcarbonyl)-6-chloropyridazine (45 mg, 0.23 mmol), 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide

(70 mg, 0.23 mmol) and potassium carbonate (63 mg, 0.46 mmol) in acetonitrile (3 mL) was stirred in a Smith Creator microwave at 130°C for 1 hour. The solid was filtered off and the solvent was removed *in vacuo*. The residue was purified by reverse phase preparative HPLC, eluting with 5 – 95% acetonitrile in water (+ 0.2% TFA), followed by passage through a Silicycle Si-Carbonate cartridge, eluting with methanol, to give the desired product as a colourless solid (97 mg). ^{1}H NMR δ ($CDCl_3$): 1.34 (3H, d), 1.66 (3H, s), 2.33 - 2.41 (2H, m), 3.40 (3H, s), 3.48 - 3.52 (1H, m), 3.56 - 3.60 (1H, m), 3.79 (3H, s), 4.27 (2H, d), 4.58 - 4.62 (1H, m), 4.76 (2H, t), 6.79 (1H, d), 6.97 (1H, t), 7.25 - 7.29 (3H, m), 7.35 - 7.36 (1H, m), 8.26 - 8.28 (1H, m), 8.49 (1H, s); *m/z* 467 $(M+H)^+$.

The preparation of 3-hydroxy-5-[(1*S*)-2-methoxy-(1-methylethyl)oxy]-*N*-(1-methyl-1*H*-pyrazol-3-yl)benzamide was described earlier.

The preparation of 3-(azetidin-1-ylcarbonyl)-6-chloropyridazine is decribed below:

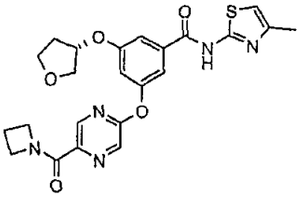
3-(Azetidin-1-ylcarbonyl)-6-chloropyridazine



Phosphorus oxychloride (50 mL) was added to 6-hydroxypyridazine-3-carboxylic acid (9.82 g, 70.05 mmol) and the resulting solution heated to reflux. After 45 mins the solution was allowed to cool and the excess of phosphorus oxychloride was removed under reduced pressure. THF (50 mL) was added to the black residue and the resulting solution cooled to 0°C. Triethylamine (9.77 mL, 70.05 mmol) and azetidine (4.0 g, 70.05 mmol) were added dropwise. The resulting mixture was allowed to warm to RT and stirred overnight. The volatiles were removed under reduced pressure and water (50 mL) added, then the residue was adjusted to pH8 using sodium hydroxide solution. The aqueous layer was extracted five times with ethyl acetate, the combined organics dried ($MgSO_4$) and the solvent removed to give the crude product as a dark oil. A sample was purified by preparative HPLC, eluting with 5 – 95% acetoniltrile in water (+ 0.2% TFA), and gave the title compound as a colorless solid (135 mg).

^{1}H NMR δ ($CDCl_3$): 2.39 - 2.47 (2H, m), 4.30 (2H, t), 4.82 (2H, t), 7.64 (1H, d), 8.21 (1H, d); *m/z* 198 $(M+H)^+$.

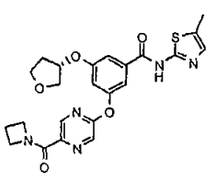
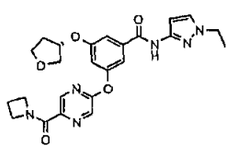
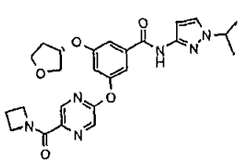
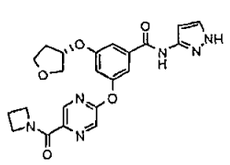
Example 43: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide

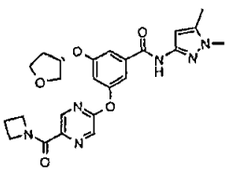


3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid (200 mg, 0.52 mmol), HATU (475 mg, 1.25 mmol) and 2-amino-4-methylthiazole (119 mg, 1.04 mmol) were suspended in DMF (2 mL). DIPEA (0.220 mL, 1.26 mmol) was then added and the reaction mixture stirred at RT for 16 hours. The DMF was removed *in vacuo* and water (15 mL) added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the extracts combined, washed with water (15 mL), 1N hydrochloric acid (10 mL), water (10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 60-100% ethyl acetate in isohexane, to give the desired compound (70 mg).

^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.32 (s, 3H), 2.34 - 2.42 (m, 2H), 3.89 - 4.02 (m, 4H), 4.26 (t, 2H), 4.69 (t, 2H), 4.96 - 4.99 (m, 1H), 6.57 (d, 1H), 6.94 (t, 1H), 7.29 (t, 1H), 7.33 (t, 1H), 8.35 (d, 1H), 8.85 (d, 1H), 9.72 (s, 1H); *m/z* 482 $(M+H)^+$, 480 $(M-H)^-$

The following compounds were prepared in an analogous fashion from 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid and the appropriate aminoheterocycle.

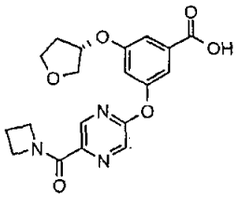
Example	Structure	m/z	NMR
43a		482 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 2.38 (s, 3H), 3.88 - 4.02 (m, 4H), 4.26 (t, 2H), 4.68 (t, 2H), 4.96 - 5.00 (m, 1H), 6.93 (t, 1H), 6.98 (s, 1H), 7.34 (t, 1H), 7.37 (t, 1H), 8.34 (d, 1H), 8.84 (d, 1H)
43b		479 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.46 (t, 3H), 2.13 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.88 - 4.02 (m, 4H), 4.06 (q, 2H), 4.26 (t, 2H), 4.69 (t, 2H), 4.96 - 5.00 (m, 1H), 6.78 (d, 1H), 6.88 (t, 1H), 7.24 (t, 1H), 7.30 - 7.31 (m, 1H), 7.32 (d, 1H), 8.34 (d, 1H), 8.36 (s, 1H), 8.86 (d, 1H)
43c		493 $(M+H)^+$ 491 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 1.48 (d, 6H), 2.13 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.88 - 4.02 (m, 4H), 4.26 (t, 2H), 4.36 (septet, 1H), 4.69 (t, 2H), 4.97 - 5.00 (m, 1H), 6.77 (d, 1H), 6.88 (t, 1H), 7.24 - 7.25 (m, 1H), 7.31 - 7.31 (m, 1H), 7.35 (d, 1H), 8.33 (d, 1H), 8.34 (s, 1H), 8.86 (d, 1H)
43d*		451 $(M+H)^+$ 449 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.88 - 4.02 (m, 4H), 4.26 (t, 2H), 4.69 (t, 2H), 4.96 - 5.00 (m, 1H), 6.84 (s, 1H), 6.87 (t, 1H), 7.28 (t, 1H), 7.31 (t, 1H), 7.46 (d, 1H), 8.36 (d, 1H), 8.83 (d, 1H), 9.45 (s, 1H), 10.05 (s, 1H)

43e		479 $(M+H)^+$ 477 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.11 - 2.24 (m, 2H), 2.26 (s, 3H), 2.33 - 2.41 (m, 2H), 3.61 (s, 3H), 3.87 - 4.00 (m, 4H), 4.25 (t, 2H), 4.68 (t, 2H), 4.93 - 4.97 (m, 1H), 6.58 (s, 1H), 6.86 (t, 1H), 7.24 (t, 1H), 7.28 (s, 1H), 8.32 (d, 1H), 8.84 (d, 1H), 8.85 (s, 1H)

* The reaction was carried out using 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate as the amino heterocycle, the resultant product was dissolved in acetonitrile and heated in a microwave reactor at 150°C for 5 - 10 minutes. The mixtures were allowed to cool then concentrated *in vacuo* to give the desired products. The preparation of 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate was described earlier.

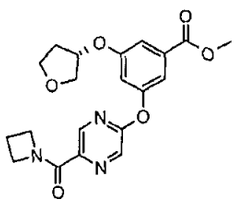
The preparation of 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid is described below:

3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid



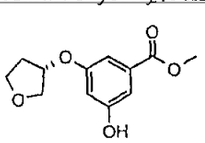
Methyl 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (7.02 mmol) was dissolved in THF (50 mL), 1N sodium hydroxide (7.0 mL) was added followed by water (50 mL) and the resultant solution stirred at RT for 4 hours. The organics were removed *in vacuo*, the aqueous solution filtered and extracted with ethyl acetate (30 mL). The aqueous layer was acidified with 2N hydrochloric acid, extracted with ethyl acetate (3 x 50 mL), and the organic extracts washed with water (10 mL), brine (10 mL) then evaporated to dryness to give the desired material as a white foam (2.33 g). ^{1}H NMR δ ($CDCl_3$): 2.14 - 2.30 (m, 2H), 2.34 - 2.42 (m, 2H), 3.89 - 3.94 (m, 2H), 3.97 - 4.02 (m, 2H), 4.28 (t, 2H), 4.69 (t, 2H), 4.97 - 5.00 (m, 1H), 6.94 (t, 1H), 7.48 (t, 2H), 8.34 (d, 1H), 8.85 (d, 1H); *m/z* 386 $(M+H)^+$, 384 $(M-H)^-$

Methyl 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate



A solution of methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (2.5 g, 10.5 mmol), potassium carbonate (2.9 g, 21.0 mmol) and 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (2.48 g, 12.6 mmol) in DMA (25 mL) was heated at 120°C for 2 hours. The solution was diluted with ethyl acetate (150 mL), washed with water (3 x 50 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on silica, eluting with 0-50% ethyl acetate in isohexane, to give the desired compound as a colourless oil (2.8 g). ^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.34 - 2.41 (m, 2H), 3.88 - 4.04 (m, 4H), 3.90 (s, 3H), 4.25 (t, 2H), 4.68 (t, 2H), 4.96 - 5.00 (m, 1H), 6.91 (t, 1H), 7.43 (d, 2H), 8.32 (d, 1H), 8.85 (d, 1H); *m/z* 386 $(M+H)^+$, 384 $(M-H)^-$

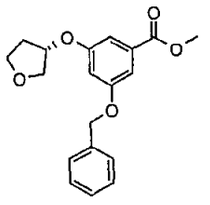
Methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate



Methyl 3-[(phenylmethyl)oxy]-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (25.0 g, 76.2 mmol) was dissolved in THF (150 mL) and ethanol (150 mL). 10% Palladium on carbon (30 mg) was added and the mixture placed under a hydrogen atmosphere and left to stir at RT until the reaction was complete. The catalyst was removed by filtration through diatomaceous earth and the filtrate was concentrated *in vacuo* to give an orange oil which crystallised on standing. The solid was filtered off and washed with diethyl ether to give the desired product as a white solid (13.75 g).

^{1}H NMR δ ($CDCl_3$): 2.1-2.3 (2H, m), 3.9 (3H, s), 3.9-3.95 (2H, m), 3.97-4.05 (2H, m), 4.95 (1H, s), 5.6 (1), 6.6 (1H, t), 7.1 (1H, t), 7.13 (1H, t); *m/z* 237 $(M+H)^+$

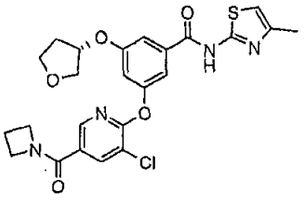
Methyl 3-[(phenylmethyl)oxy]-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate



A mixture of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (18.8 g, 72.75 mmol), (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (18.5 g, 76.4 mmol) and potassium carbonate (20.08 g, 145.5 mmol) in butyronitrile (250 mL) was heated to 130°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate added. The organics were washed with water (40 mL), 0.5M sodium hydroxide solution (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 0-5% methanol in DCM, to give the desired compound as a colourless oil (20.1 g). ^{1}H NMR δ ($CDCl_3$): 2.08 - 2.26 (m, 2H), 3.78 - 4.01 (m, 4H), 3.90 (s, 3H), 4.92 - 4.96 (m, 1H), 5.08 (s, 2H), 6.69 (t, 1H), 7.15 (t, 1H), 7.29 (t, 1H), 7.34 - 7.44 (m, 5H); *m/z* 327 $(M+H)^+$

The preparations of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate and (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate were described earlier.

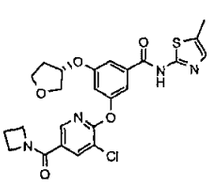
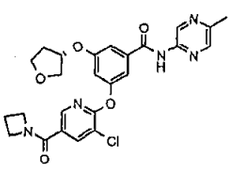
Example 44: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-*N*-(4-methyl-1,3-thiazol-2-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide

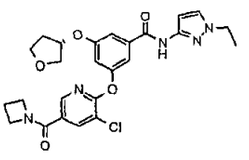
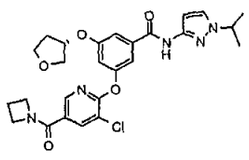
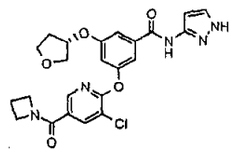


1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.70 mL, 0.53 mmol) was added to a solution of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid (200 mg, 0.48 mmol) in DCM (6 mL) and stirred at RT for 2 hours. 2-Amino-4-methylthiazole (110 mg, 0.96 mmol) and pyridine (0.078 mL, 0.96 mmol) were added and the reaction stirred at RT for 16 hours. The solvent was removed *in vacuo*, water

(20 mL) added and the mixture extracted with ethyl acetate (3 x 20 mL). The extracts were combined and washed with 2N hydrochloric acid (20 mL), saturated aqueous sodium bicarbonate solution (20 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 50-100% ethyl acetate in isohexane, to give the desired compound (78 mg).
^{1}H NMR δ ($CDCl_3$): 2.13 - 2.28 (m, 2H), 2.31 (s, 3H), 2.35 - 2.43 (m, 2H), 3.88 - 4.02 (m, 4H), 4.21 - 4.28 (m, 2H), 4.31 - 4.39 (m, 2H), 4.96 - 5.00 (m, 1H), 6.56 (d, 1H), 6.94 (t, 1H), 7.28 (t, 1H), 7.34 (t, 1H), 8.16 (d, 1H), 8.25 (d, 1H), 9.83 (s, 1H); *m/z* 515 $(M+H)^+$, 513 $(M-H)^-$

The following compounds were prepared in an analogous fashion from 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid and the appropriate aminoheterocycle.

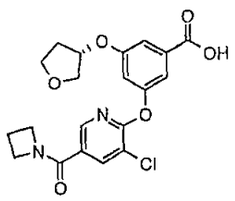
Example	Structure	m/z	NMR
44a		515 $(M+H)^+$ 513 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 2.38 (s, 3H), 3.88 - 4.02 (m, 4H), 4.24 - 4.34 (m, 4H), 4.96 - 4.99 (m, 1H), 6.94 (t, 1H), 6.97 (d, 1H), 7.34 (t, 1H), 7.36 - 7.37 (m, 1H), 8.15 (d, 1H), 8.24 (d, 1H), 10.82 (s, 1H)
44b		510 $(M+H)^+$ 508 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.15 - 2.31 (m, 2H), 2.35 - 2.43 (m, 2H), 2.56 (s, 3H), 3.89 - 4.03 (m, 4H), 4.20 - 4.39 (m, 4H), 4.99 - 5.03 (m, 1H), 6.93 (t, 1H), 7.29 (t, 1H), 7.35 (t, 1H), 8.14 (s, 1H), 8.16 (d, 1H), 8.26 (d, 1H), 8.36 (s, 1H), 9.54 (d, 1H)

44c		512 $(M+H)^+$ 510 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 1.46 (t, 3H), 2.14 - 2.30 (m, 2H), 2.35 - 2.43 (m, 2H), 3.88 - 4.02 (m, 4H), 4.06 (q, 2H), 4.20 - 4.28 (m, 2H), 4.31 - 4.39 (m, 2H), 4.97 - 5.01 (m, 1H), 6.78 (d, 1H), 6.89 (t, 1H), 7.23 (t, 1H), 7.30 - 7.31 (m, 1H), 7.32 (d, 1H), 8.16 (d, 1H), 8.25 (d, 1H), 8.37 (s, 1H)
44d		526 $(M+H)^+$ 524 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 1.48 (d, 6H), 2.14 - 2.29 (m, 2H), 2.35 - 2.43 (m, 2H), 3.88 - 4.02 (m, 4H), 4.20 - 4.28 (m, 2H), 4.30 - 4.40 (m, 2H), 4.36 (septet, 1H), 4.98 - 5.01 (m, 1H), 6.78 (d, 1H), 6.89 (t, 1H), 7.24 (t, 1H), 7.32 (t, 1H), 7.35 (d, 1H), 8.16 (d, 1H), 8.25 (d, 1H), 8.35 (s, 1H)
44e*		484 $(M+H)^+$ 482 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.87 - 4.02 (m, 4H), 4.20 - 4.28 (m, 2H), 4.29 - 4.37 (m, 2H), 4.97 - 5.00 (m, 1H), 6.85 (s, 1H), 6.88 (t, 1H), 7.29 - 7.30 (m, 1H), 7.31 - 7.31 (m, 1H), 7.44 (d, 1H), 8.15 (d, 1H), 8.21 (d, 1H), 9.76 (s, 1H), 10.17 (s, 1H)

* The reaction was carried out using 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate as the amino heterocycle, the resultant product was dissolved in acetonitrile and heated in a microwave reactor at 150°C for 5 - 10 minutes. The mixtures were allowed to cool then concentrated *in vacuo* to give the desired products. The preparation of 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate was described earlier.

The preparation of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid is described below:

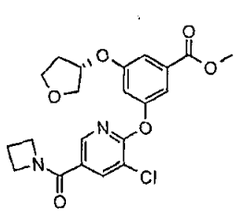
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid



Methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (3.75 g, 8.68 mmol) was dissolved in THF (40 mL), 1N sodium hydroxide (8.68 mL, 8.68 mmol) was added followed by water (40 mL) and methanol (1 drop) and the resultant solution stirred at RT for 3 hours. The organics were removed *in vacuo*, the aqueous solution filtered and extracted with ethyl acetate (30 mL). The aqueous layer was acidified with 2N hydrochloric acid, extracted with ethyl acetate (3 x 50 mL), and the organic extracts washed with water (10 mL), brine (10 mL) then evaporated to dryness to give the desired material as a white foam (3.53 g).

^{1}H NMR δ ($CDCl_3$): 2.14 - 2.30 (m, 2H), 2.35 - 2.43 (m, 2H), 3.89 - 3.94 (m, 2H), 3.96 - 4.02 (m, 2H), 4.22 - 4.38 (m, 4H), 4.97 - 5.01 (m, 1H), 6.95 (t, 1H), 7.46 - 7.47 (m, 1H), 7.49 - 7.50 (m, 1H), 8.15 (d, 1H), 8.26 (d, 1H); *m/z* 419 $(M+H)^+$, 417 $(M-H)^-$.

Methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate

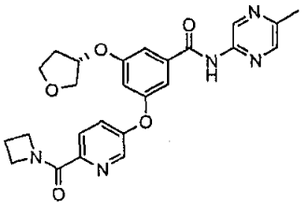


A solution of methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (2.5 g, 10.5 mmol), potassium carbonate (2.9 g, 21.0 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (2.9 g, 12.6 mmol) in DMA (25 mL) was heated at 120°C for 5 hours. The solution was diluted with ethyl acetate (150 mL), washed with water (3 x 50 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was purified by chromatography on silica, eluting with 20-50% ethyl acetate in isohexane, to

give the desired compound as a colourless oil (3.75 g). ^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.38 (quin, 2H), 3.85 - 4.04 (m, 4H), 3.90 (s, 3H), 4.19 - 4.37 (m, 4H), 4.96 - 5.00 (m, 1H), 6.91 (t, 1H), 7.42 - 7.45 (m, 2H), 8.14 (d, 1H), 8.25 (d, 1H); *m/z* 433 $(M+H)^+$.

The preparations of methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine were described earlier.

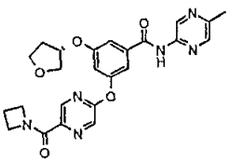
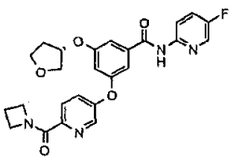
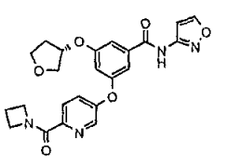
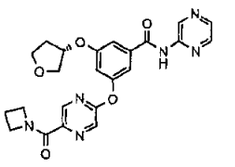
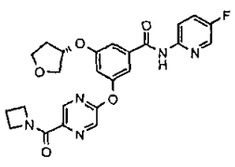
Example 45: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-*N*-(5-methylpyrazin-2-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.133 mL, 1.0 mmol) was added to a suspension of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid (350 mg, 0.94 mmol) in DCM (10 mL) and stirred at RT for 30min. 2-Amino-5-methylpyrazine (196 mg, 1.82 mmol) and pyridine (0.148 mL, 1.82 mmol) were added and the reaction stirred at RT for 2 hours. The solvent was removed *in vacuo* and water (30 mL) added. The mixture was extracted with ethyl acetate (3 x 20 mL), washed with 2N hydrochloric acid (20 mL), water (10 mL), saturated aqueous sodium bicarbonate solution (20 mL), water (10 mL) and brine (20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by chromatography, eluting with 0-10% methanol in DCM, to give the desired product as a colourless oil (150 mg). ^{1}H NMR δ ($CDCl_3$): 2.12 - 2.18 (1H, m), 2.22 - 2.29 (1H, m), 2.31 - 2.40 (2H, m), 2.56 (3H, s), 3.89 - 4.03 (4H, m), 4.25 (2H, t), 4.71 (2H, t), 4.97 - 5.00 (1H, m), 6.76 (1H, t), 7.15 (1H, t), 7.25 (1H, d), 7.38 - 7.40 (1H, m), 8.12 (1H, s), 8.14 (1H, d), 8.32 (1H, s), 8.34 (1H, d), 9.52 (1H, d); *m/z* 476 $(M+H)^+$, 474 $(M-H)^-$

The following compound was prepared in an analogous fashion from 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid or 3-{[6-

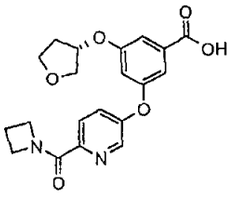
(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid and the appropriate aminoheterocycle.

Example	Structure	m/z	NMR
45a		477 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.16 - 2.31 (m, 2H), 2.34 - 2.42 (m, 2H), 2.56 (s, 3H), 3.89 - 4.02 (m, 4H), 4.26 (t, 2H), 4.69 (t, 2H), 4.98 - 5.02 (m, 1H), 6.92 (s, 1H), 7.30 (s, 1H), 7.35 (s, 1H), 8.15 (s, 1H), 8.36 (s, 2H), 8.86 (s, 1H), 9.54 (s, 1H)
45b		479 $(M+H)^+$ 477 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.31 (m, 2H), 2.32 - 2.40 (m, 2H), 3.90 - 4.04 (m, 4H), 4.26 (t, 2H), 4.71 (t, 2H), 4.97 - 5.01 (m, 1H), 6.76 (t, 1H), 7.13 (t, 1H), 7.23 (t, 1H), 7.39 (dd, 1H), 7.48 - 7.53 (m, 1H), 8.14 (d, 1H), 8.16 (d, 1H), 8.33 - 8.38 (m, 2H), 8.47 (s, 1H)
45c		451 $(M+H)^+$ 449 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.13 - 2.31 (m, 2H), 2.32 - 2.39 (m, 2H), 3.89 - 4.03 (m, 4H), 4.25 (t, 2H), 4.71 (t, 2H), 4.97 - 5.01 (m, 1H), 6.79 (t, 1H), 7.18 (d, 1H), 7.22 (t, 1H), 7.27 (t, 1H), 7.37 (dd, 1H), 8.11 (d, 1H), 8.28 (d, 1H), 8.33 (d, 1H), 9.47 (s, 1H)
45d		463 $(M+H)^+$ 461 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.15 - 2.32 (m, 2H), 2.35 - 2.43 (m, 2H), 3.90 - 4.06 (m, 4H), 4.27 (t, 2H), 4.70 (t, 2H), 5.00 - 5.05 (m, 1H), 6.93 (t, 1H), 7.31 (t, 1H), 7.36 (t, 1H), 8.29 (t, 1H), 8.38 - 8.38 (m, 1H), 8.40 - 8.41 (m, 1H), 8.46 (s, 1H), 8.86 (d, 1H), 9.68 (s, 1H)
45e		480 $(M+H)^+$ 478 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.15 - 2.31 (m, 2H), 2.35 - 2.43 (m, 2H), 3.90 - 4.03 (m, 4H), 4.27 (t, 2H), 4.69 (t, 2H), 4.99 - 5.02 (m, 1H), 6.91 (t, 1H), 7.28 (t, 1H), 7.33 (t, 1H), 7.48 - 7.53 (m, 1H), 8.16 (d, 1H), 8.35 - 8.39 (m, 1H), 8.37 (d, 1H), 8.51 (s, 1H), 8.86 (d, 1H)

The preparation of 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid was described earlier.

The preparation of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid is described below:

3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid

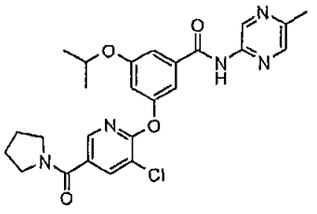


Methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate (875 mg, 3.68 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (1.06 g, 4.41 mmol), caesium carbonate (3.59 g, 11.03 mmol), and bromotris(triphenylphosphine)copper (0.69 g, 0.735 mmol) were added together in DMA (16 mL) and heated in a microwave reactor at 160°C for 9 hours. The mixture was taken up in water (25 mL) and washed with ethyl acetate (2 x 20 mL). The aqueous layer was acidified with 1N hydrochloric acid (30 mL) and extracted with ethyl acetate (5 x 30 mL). The combined organic extract was washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and evaporated to give a brown solid which was triturated with diethyl ether to give the desired compound as a beige solid (820 mg).

^{1}H NMR δ (d_6-DMSO): 2.00 - 2.06 (m, 1H), 2.23 - 2.37 (m, 3H), 3.78 - 3.95 (m, 4H), 4.13 (t, 2H), 4.64 (t, 2H), 5.16 - 5.19 (m, 1H), 7.05 (t, 1H), 7.18 - 7.19 (m, 1H), 7.33 - 7.34 (m, 1H), 7.62 (dd, 1H), 8.04 (d, 1H), 8.46 (d, 1H); *m/z* 385 $(M+H)^+$, 383 $(M-H)^-$

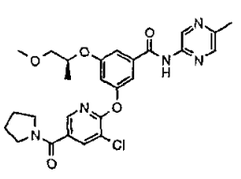
The preparations of methyl 3-hydroxy-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoate and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine were described earlier.

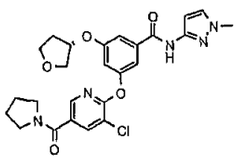
Example 46: 3-{[3-Chloro-5-(pyrrolidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



Cesium carbonate (782 mg, 2.4 mmol) was added to a solution of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (230 mg, 0.8 mmol) and 2,3-dichloro-5-(pyrrolidin-1-ylcarbonyl)pyridine (234 mg, 0.96 mmol) in acetonitrile (5 mL) and the stirred mixture heated in a microwave reactor at 120°C for 2 hours. The mixture was cooled to RT and the acetonitrile evaporated *in vacuo*. The residue was partitioned between water (25 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 75% ethyl acetate in isohexane, to give the desired compound (290 mg).
^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 1.9 (m, 4H), 2.5 (s, 3H), 3.4-3.7 (m, 4H), 4.55 (m, 1H), 6.85 (d, 1H), 7.2 (d, 1H), 7.25 (d, 1H), 7.9 (d, 1H), 8.1 (dd, 1H), 8.2 (s, 1H), 8.35 (s, 1H) and 9.45 (s, 1H); *m/z* 496 $(M+H)^+$.

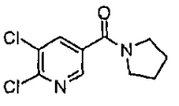
The following compounds were prepared in an analogous fashion from 2,3-dichloro-5-(pyrrolidin-1-ylcarbonyl)pyridine and either 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide or 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide.

Example	Structure	m/z	NMR
46a		526 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 1.9 (m, 4H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 – 3.6 (m, 6H), 4.55 (m, 1H), 6.9 (d, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 7.95 (d, 1H), 8.05 (s, 1H), 8.15 (d, 1H), 8.35 (s, 1H), 9.5 (s, 1H).

46b		512 $(M+H)^+$	1H NMR δ ($CDCl_3$): 1.8 – 1.95 (m, 4H), 2.1 (m, 2H), 3.45 (t, 2H), 3.6 (t, 2H), 3.7 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.9 (m, 1H), 6.7 (d, 1H), 6.8 (d, 1H), 7.15 (d, 1H), 7.25 (d, 2H), 7.95 (d, 1H), 8.1 (d, 1H), 8.9 (s, 1H)

The preparation of 2,3-dichloro-5-(pyrrolidin-1-ylcarbonyl)pyridine is described below:

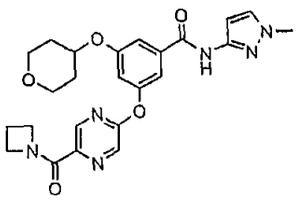
2,3-Dichloro-5-(pyrrolidin-1-ylcarbonyl)pyridine



Oxalyl chloride (3.2 mL; 36.0 mmol) was added to a solution of 5,6 dichloronicotinic acid (5.76 g; 30.0 mmol) and 4M hydrogen chloride in dioxan (7.5 mL; 30.0 mmol) in DCM (50 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*, the residue azeotroped with toluene (2 x 15 mL) then added to a solution of pyrrolidine (3.0 mL; 36.0 mmol) and triethylamine (10.0 mL; 72 mmol) in DCM (150 mL). The mixture was stirred at RT for 6 hours, the DCM evaporated *in vacuo*, the residue partitioned between water (75 mL) and ethyl acetate (100 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired compound which was further purified by crystallisation from ethyl acetate and isohexane (6.88 g). ^{1}H NMR δ ($CDCl_3$): 1.9 (m, 4H), 3.4 (m, 2H), 3.6 (s, 3H), 7.9 (s, 1H) and 8.4 (s, 1H); *m/z* 245 $(M+H)^+$.

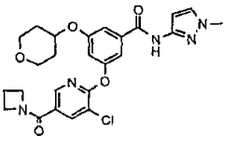
The preparations of 3-hydroxy-5-[(1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide and 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide were described earlier.

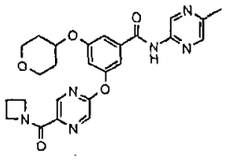
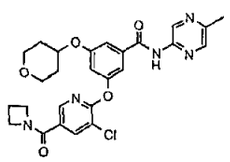
Example 47: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide (209 mg, 0.66 mmol), 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (159 mg, 0.80 mmol) and potassium carbonate (184 mg, 1.33 mmol) were dissolved / suspended in acetonitrile (3.5 mL). The reaction mixture was heated in a microwave reactor for 4 hours at 120°C then cooled, filtered and reduced *in vacuo*. The crude product was purified by chromatography on silica, eluting with 0-5% methanol in DCM, to give the required product as a white foam (39 mg). ^{1}H NMR δ (d_6-DMSO): 1.57 - 1.68 (m, 2H), 1.97 - 2.05 (m, 2H), 2.26 - 2.36 (m, 2H), 3.47 - 3.55 (m, 2H), 3.78 (s, 3H), 3.84 - 3.91 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.67 - 4.75 (m, 1H), 6.58 (d, 1H), 7.11 (t, 1H), 7.43 (t, 1H), 7.54 (t, 1H), 7.60 (d, 1H), 8.56 (d, 1H), 8.68 (d, 1H), 10.80 (s, 1H); *m/z* 479 (M+H)+

The following compounds were made in an analogous fashion from the either 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide or 3-hydroxy-*N*-(5-methylpyrazin-2-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide and the appropriate halogenated heterocycle.

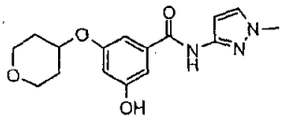
Example	Structure	m/z	NMR
47a		512 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.57 - 1.67 (m, 2H), 1.98 - 2.06 (m, 2H), 2.21 - 2.32 (m, 2H), 3.47 - 3.55 (m, 2H), 3.78 (s, 3H), 3.84 - 3.91 (m, 2H), 4.01 - 4.10 (m, 2H), 4.33 - 4.41 (m, 2H), 4.67 - 4.75 (m, 1H), 6.57 (d, 1H), 7.09 (t, 1H), 7.40 (t, 1H), 7.52 (t, 1H), 7.60 (d, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 10.79 (s, 1H)

47b		491 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.58 - 1.68 (m, 2H), 1.99 - 2.06 (m, 2H), 2.26 - 2.35 (m, 2H), 2.49 (s, 3H), 3.47 - 3.55 (m, 2H), 3.84 - 3.91 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.69 - 4.77 (m, 1H), 7.18 (t, 1H), 7.49 (t, 1H), 7.58 (t, 1H), 8.36 (d, 1H), 8.57 (d, 1H), 8.68 (d, 1H), 9.25 (d, 1H), 10.98 (s, 1H)
47c		524 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.63 (m, 2H), 2.02 (m, 2H), 2.27 (m, 2H), 2.49 (s, 3H), 3.51 (m, 2H), 3.87 (m, 2H), 4.06 (t, 2H), 4.36 (t, 2H), 4.74 (m, 1H), 7.16 (t, 1H), 7.47 (t, 1H), 7.57 (t, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 8.36 (m, 1H), 9.25 (d, 1H), 10.98 (s, 1H)

The preparations of 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine were described earlier.

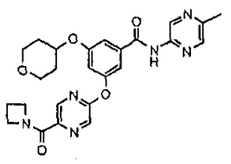
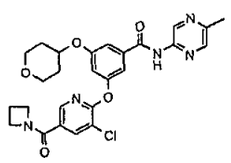
The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide is described below:

3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



N-(1-Methyl-1*H*-pyrazol-3-yl)-3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide (1.85 g, 4.54 mmol) was dissolved in ethanol (40 mL) and 10% palladium on charcoal (97 mg) catalyst added under argon. The reaction was stirred under an atmosphere of hydrogen for 16 hours then filtered through Celite® and the filtrate concentrated *in vacuo* give the desired compound as a light brown solid (1.30 g).

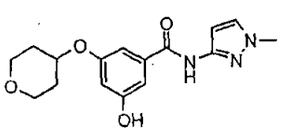
^{1}H NMR δ (d_6-DMSO): 1.54 - 1.65 (m, 2H), 1.94 - 2.03 (m, 2H), 3.44 - 3.54 (m, 2H), 3.78 (s, 3H), 3.83 - 3.90 (m, 2H), 4.56 - 4.65 (m, 1H), 6.51 (t, 1H), 6.56 (d, 1H), 6.97 (t, 1H), 7.08 (t, 1H), 7.59 (d, 1H), 9.63 (s, 1H), 10.59 (s, 1H); *m/z* 318 $(M+H)^+$

47b		491 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.58 - 1.68 (m, 2H), 1.99 - 2.06 (m, 2H), 2.26 - 2.35 (m, 2H), 2.49 (s, 3H), 3.47 - 3.55 (m, 2H), 3.84 - 3.91 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.69 - 4.77 (m, 1H), 7.18 (t, 1H), 7.49 (t, 1H), 7.58 (t, 1H), 8.36 (d, 1H), 8.57 (d, 1H), 8.68 (d, 1H), 9.25 (d, 1H), 10.98 (s, 1H)
47c		524 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.63 (m, 2H), 2.02 (m, 2H), 2.27 (m, 2H), 2.49 (s, 3H), 3.51 (m, 2H), 3.87 (m, 2H), 4.06 (t, 2H), 4.36 (t, 2H), 4.74 (m, 1H), 7.16 (t, 1H), 7.47 (t, 1H), 7.57 (t, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 8.36 (m, 1H), 9.25 (d, 1H), 10.98 (s, 1H)

The preparations of 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine were described earlier.

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide is described below:

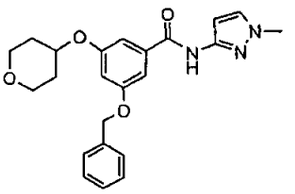
3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



N-(1-Methyl-1*H*-pyrazol-3-yl)-3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide (1.85 g, 4.54 mmol) was dissolved in ethanol (40 mL) and 10% palladium on charcoal (97 mg) catalyst added under argon. The reaction was stirred under an atmosphere of hydrogen for 16 hours then filtered through Celite® and the filtrate concentrated *in vacuo* give the desired compound as a light brown solid (1.30 g).

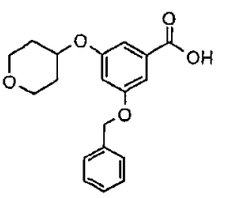
^{1}H NMR δ (d_6-DMSO): 1.54 - 1.65 (m, 2H), 1.94 - 2.03 (m, 2H), 3.44 - 3.54 (m, 2H), 3.78 (s, 3H), 3.83 - 3.90 (m, 2H), 4.56 - 4.65 (m, 1H), 6.51 (t, 1H), 6.56 (d, 1H), 6.97 (t, 1H), 7.08 (t, 1H), 7.59 (d, 1H), 9.63 (s, 1H), 10.59 (s, 1H); *m/z* 318 $(M+H)^+$

N-(1-Methyl-1*H*-pyrazol-3-yl)-3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



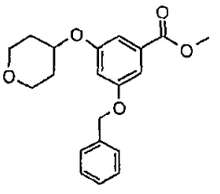
3-[(Phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzoic acid (3.14 g, 9.5 mmol), 1-methyl-1*H*-pyrazol-3-amine (1.85 g, 19.0 mmol) and HATU (4.70 g, 12.35 mmol) were dissolved in DMF (12.5 mL) and DIPEA (3.31 mL, 19.0 mmol) added. The resultant mixture was stirred at RT for 20 hours. The mixture was quenched with water (150 mL), extracted with ethyl acetate (2 x 75 mL), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 0-50% ethyl acetate in isohexane, to give the desired compound as a pale yellow gum (1.85 g).

3-[(Phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzoic acid



Methyl 3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzoate (9.00 g, 26.3 mmol) was dissolved in THF (120 mL) and methanol (30 mL) added a solution of lithium hydroxide monohydrate (3.24 g, 78.9 mmol) in water (60 mL). The bi-phasic solution was stirred at RT for 3 hours until complete conversion was indicated by LCMS. The organics were removed *in vacuo* and water (40 mL) added. The pH of the mixture was adjusted to 7 by the addition of hydrochloric acid and the resulting precipitate filtered and washed with cold water to give the desired compound as a white solid (8.03 g). ^{1}H NMR δ (d_6-DMSO): 1.57 (m, 2H), 1.94 (m, 2H), 3.50 (m, 2H), 3.84 (m, 2H), 4.62 (m, 1H), 5.15 (s, 2H), 6.87 (t, 1H), 7.09 (m, 1H), 7.14 (m, 1H), 7.34 (t, 1H), 7.40 (t, 2H), 7.46 (d, 2H), 12.99 (s, 1H); *m/z* 327 $(M+H)^+$

Methyl 3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzoate

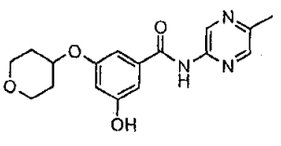


Methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate (7.75 g, 30.0 mmol), tetrahydro-4*H*-pyra-4-ol (4.28 mL, 45.0 mmol) and triphenylphosphine (11.8 g, 45.0 mmol) were stirred under argon in THF (166 mL) and cooled to 5°C in an ice bath. DEAD (19.6 mL, 45.0 mmol) was added dropwise to the mixture, maintaining the internal temperature below 10°C. Stirring was continued for 16 hours then the reaction mixture reduced in vacuo and the residue redissolved in ethyl acetate (60 mL) and isohexane (60 mL). The precipitate was removed, the filtrate concentrated in vacuo and purified by chromatography on silica, eluting with 0-25% ethyl acetate in isohexane (a small quantity of DCM used to assist column loading), to give the desired compound as a colourless oil (9.0 g).

^{1}H NMR δ (d_6-DMSO): 1.58 (m, 2H), 1.94 (m, 2H), 3.49 (m, 2H), 3.84 (m, 5H), 4.65 (m, 1H), 5.16 (s, 2H), 6.92 (t, 1H), 7.10 (m, 1H), 7.15 (m, 1H), 7.34 (t, 1H), 7.40 (t, 2H), 7.46 (d, 2H); *m/z* 343 $(M+H)^+$

The preparation of methyl 3-hydroxy-5-{[phenylmethyl]oxy}benzoate was described earlier. The preparation of 3-hydroxy-*N*-(5-methylpyrazin-2-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide is described below:

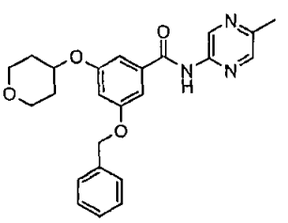
3-Hydroxy-*N*-(5-methylpyrazin-2-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



N-(5-Methylpyrazin-2-yl)-3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide (1.70 g, 4.05 mmol) was dissolved in ethanol (40 mL) and 10% palladium on charcoal (86 mg) catalyst added under argon. The reaction was stirred under

an atmosphere of hydrogen for 4 days then filtered and the filtrate concentrated *in vacuo* to give the desired compound as a cream-coloured solid (1.20 g). *m/z* 330 $(M+H)^+$

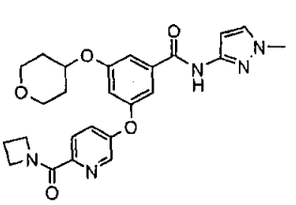
N-(5-Methylpyrazin-2-yl)-3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



3-[(Phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzoic acid (3.14 g, 9.5 mmol), 2-amino-5 methylpyrazine (2.08 g, 19.0 mmol) and HATU (4.70 g, 12.35 mmol) were dissolved in DMF (12.5 mL) and DIPEA (3.31 mL, 19.0 mmol) added. The resultant mixture was stirred at RT for 20 hours. The mixture was quenched with water (150 mL) and extracted with ethyl acetate (2 x 75 mL), washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica, eluting with 0-50% ethyl acetate in isohexane, to give the desired compound as a pale yellow gum (1.70 g). *m/z* 420 $(M+H)^+$

The preparations of 3-[(phenylmethyl)oxy]-5-(tetrahydro-2*H*-pyran-4-yloxy)benzoic acid and 2-amino-5 methylpyrazine were described earlier.

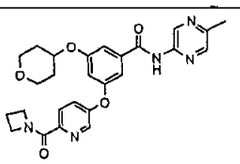
Example 48: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide



3-Hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide (200 mg, 0.63 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (184 mg, 0.76 mmol), bromotris(triphenylphosphine)copper (186 mg, 0.2 mmol) and caesium carbonate (411 mg,

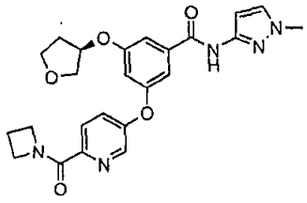
1.26 mmol) were dissolved / suspended in DMA (3.5 mL). The reaction mixture was heated in a microwave reactor for 1 hour at 200°C then allowed to cool, filtered and reduced *in vacuo*. Water (25 mL) was added and the product extracted with ethyl acetate (2 x 25 mL), the organics dried ($MgSO_4$) then purified by chromatography on silica, eluting with 0-10% methanol in DCM, to give the desired compound as a pale yellow foam (65 mg). ^{1}H NMR δ (d_6-DMSO): 1.57 - 1.67 (m, 2H), 1.97 - 2.05 (m, 2H), 2.23 - 2.34 (m, 2H), 3.51 (t, 2H), 3.78 (s, 3H), 3.83 - 3.90 (m, 2H), 4.08 (t, 2H), 4.59 (t, 2H), 4.69 - 4.76 (m, 1H), 6.56 (d, 1H), 7.00 (t, 1H), 7.29 (t, 1H), 7.49 (t, 1H), 7.54 - 7.58 (m, 1H), 7.60 (d, 1H), 8.00 (d, 1H), 8.41 (d, 1H), 10.83 (s, 1H); *m/z* 478 $(M+H)^+$

The folowing compound was made in an analogous fashion from 2-(azetidin-1-ylcarbonyl)-5-bromopyridine and 3-hydroxy-*N*-(5-methylpyrazin-2-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide.

Example	Structure	m/z	NMR
48a		490 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.62 (m, 2H), 2.01 (m, 2H), 2.28 (m, 2H), 2.48 (s, 3H), 3.50 (m, 2H), 3.86 (m, 2H), 4.07 (t, 2H), 4.59 (t, 2H), 4.75 (m, 1H), 7.08 (t, 1H), 7.49 (s, 1H), 7.53 (s, 1H), 7.56 (q, 1H), 8.00 (d, 1H), 8.36 (s, 1H), 8.43 (d, 1H), 9.24 (d, 1H), 11.09 (s, 1H)

The preparations of 2-(azetidin-1-ylcarbonyl)-5-bromopyridine, 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide and 3-hydroxy-*N*-(5-methylpyrazin-2-yl)-5-(tetrahydro-2*H*-pyran-4-yloxy)benzamide were described earlier.

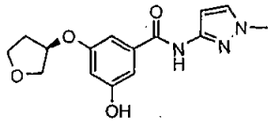
Example 49: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*R*)-tetrahydrofuran-3-yloxy]benzamide



A mixture of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*R*)-tetrahydrofuran-3-yloxy]benzamide (150 mg, 0.49 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (120 mg, 0.49 mmol), bromotris(triphenylphosphine)copper (92 mg, 0.10 mmol) and caesium carbonate (484 mg, 1.48 mmol) in acetonitrile (7 mL) was stirred in a microwave reactor at 160°C for 6 hours. The solid was filtered off, the solvent was removed *in vacuo* and ethyl acetate (50 mL) added to the residue. The organic phase was washed with water (10 mL), brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 0-10% methanol in DCM, to give the title compound as a white solid (86 mg). ^{1}H NMR δ ($CDCl_3$): 2.10 - 2.17 (m, 1H), 2.19 - 2.25 (m, 1H), 2.32 - 2.38 (m, 2H), 3.76 (s, 3H), 3.87 - 3.92 (m, 1H), 3.95 - 4.01 (m, 3H), 4.24 (t, 2H), 4.71 (t, 2H), 4.97 (t, 1H), 6.73 (t, 1H), 6.81 (s, 1H), 7.11 (s, 1H), 7.24 (s, 1H), 7.27 - 7.30 (m, 1H), 7.36 - 7.39 (m, 1H), 8.12 (d, 1H), 8.31 (d, 1H), 8.72 (s, 1H); *m/z* 464 $(M+H)^+$.

The preparation of 2-(azetidin-1-ylcarbonyl)-5-bromopyridine was described earlier.
The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*R*)-tetrahydrofuran-3-yloxy]benzamide is described below:

3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*R*)-tetrahydrofuran-3-yloxy]benzamide

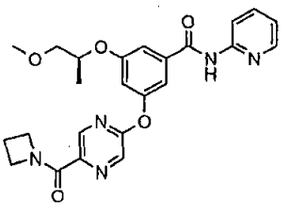


A suspension of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy]benzamide (450 mg, 1.39 mmol), (3*S*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate (507 mg, 2.09 mmol) and potassium carbonate (481 mg, 3.48

mmol) in acetonitrile (5 mL) was stirred in a microwave reactor at 160°C for 3 hours. The solvent was removed *in vacuo* and ethyl acetate added. The organics were washed with water (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 0-100% ethyl acetate in isohexane, to give *N*-(1-methyl-1*H*-pyrazol-3-yl)-3-[(phenylmethyl)oxy]-5-[(3*R*)-tetrahydrofuran-3-yloxy]benzamide as a white foam. This was dissolved in ethanol (5 mL) and ammonium formate (182 mg, 2.88 mmol) added in one portion. The reaction was blanketed with argon and 10% palladium on activated carbon (30 mg) was added. This mixture was heated in a microwave reactor at 140°C for 10 minutes, the catalyst filtered off and the volatiles removed *in vacuo* to give the title product as a white solid (305 mg). ^{1}H NMR δ (d_6-DMSO): 1.96 - 2.00 (m, 1H), 2.20 - 2.25 (m, 1H), 3.74 - 3.85 (m, 6H), 3.87 - 3.91 (m, 1H), 5.06 - 5.08 (m, 1H), 6.46 (t, 1H), 6.57 (d, 1H), 6.97 (s, 1H), 7.02 (s, 1H), 7.60 (d, 1H), 9.74 (s, 1H), 10.70 (s, 1H); *m/z* 304 $(M+H)^+$.

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(phenylmethyl)oxy] benzamide was described earlier. (3*S*)-Tetrahydrofuran-3-yl 4-methylbenzenesulfonate was prepared in an analogous fashion to (3*R*)-tetrahydrofuran-3-yl 4-methylbenzenesulfonate, as described in **Example 25**.

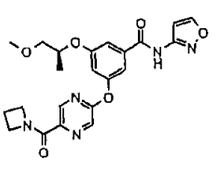
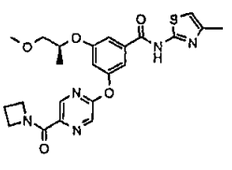
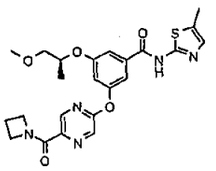
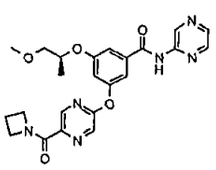
Example 50: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-pyridin-2-ylbenzamide

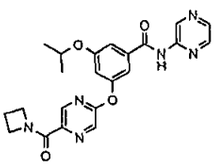
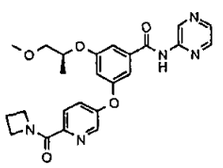
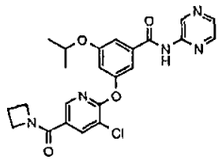
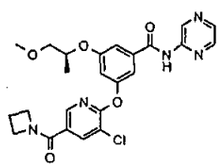


1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.080 mL, 0.6 mmol) was added to a solution of 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid (193 mg, 0.50 mmol) in DCM (10 mL) and stirred at RT for 30 minutes. 2-Aminopyridine (57 mg, 0.6 mmol) and pyridine (0.082 mL, 1 mmol) were added and the reaction stirred for a further 16 hours. The solvent was removed *in* vacu and the residue was taken up in ethyl acetate (50 mL). The organic phase was washed

with water (2 x 20 mL),1N citric acid (10 mL), water (10 mL), a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (100 mL), then dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was chromatographed on silica, eluting with a gradient of 50-80% ethyl acetate in isohexane, to give the desired compound as a white foam (42 mg). ^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.31 (quin, 2H), 3.34 (s, 3H), 3.43 - 3.56 (m, 2H), 4.19 (t, 2H), 4.57 (q, 1H), 4.62 (t, 2H), 6.90 (s, 1H), 7.03 (t, 1H), 7.20 (s, 1H), 7.36 (s, 1H), 7.71 (t, 1H), 8.23 (d, 1H), 8.28 (s, 1H), 8.30 (d, 1H), 8.64 (s, 1H), 8.79 (s, 1H); *m/z* 464 $(M+H)^+$

The following compounds were prepared in an analogous fashion from the appropriate benzoic acid and the appropriate aminoheterocycle.

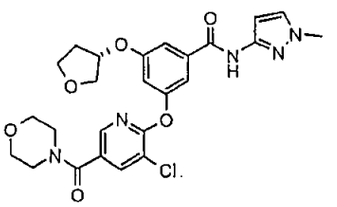
Example	Structure	m/z	NMR
50a		454 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.26 - 2.38 (m, 2H), 3.34 (s, 3H), 3.42 - 3.57 (m, 2H), 4.19 (t, 2H), 4.51 - 4.70 (m, 3H), 6.92 (s, 1H), 7.12 (s, 1H), 7.27 (s, 1H), 7.36 (s, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.78 (s, 1H), 9.33 (s, 1H)
50b		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.22 (s, 3H), 2.27 - 2.39 (m, 2H), 3.33 (s, 3H), 3.41 - 3.57 (m, 2H), 4.19 (t, 2H), 4.50 - 4.58 (m, 1H), 4.62 (t, 2H), 6.50 (s, 1H), 6.92 (s, 1H), 7.23 (s, 1H), 7.35 (s, 1H), 8.27 (s, 1H), 8.78 (s, 1H)
50c		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.25 - 2.36 (m, 5H), 3.32 (s, 3H), 3.40 - 3.54 (m, 2H), 4.19 (t, 2H), 4.52 (q, 1H), 4.61 (t, 2H), 6.81 (s, 1H), 6.92 (s, 1H), 7.28 (s, 1H), 7.38 (s, 1H), 8.25 (s, 1H), 8.77 (s, 1H)
50d		465 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 3H), 2.32 (quin, 2H), 3.34 (s, 3H), 3.44 - 3.56 (m, 2H), 4.19 (t, 2H), 4.56 (q, 1H), 4.62 (t, 2H), 6.92 (s, 1H), 7.23 (s, 1H), 7.35 (s, 1H), 8.21 (s, 1H), 8.29 (s, 1H), 8.33 (s, 1H), 8.43 (s, 1H), 8.79 (s, 1H), 9.61 (s, 1H)

50e		435 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 6H), 2.32 (quin, 2H), 4.19 (t, 2H), 4.56 (quin, 1H), 4.62 (t, 2H), 6.85 (s, 1H), 7.20 (s, 1H), 7.30 (s, 1H), 8.21 (s, 1H), 8.29 (s, 1H), 8.33 (s, 1H), 8.40 (s, 1H), 8.80 (s, 1H), 9.61 (s, 1H)
50f		464 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.29 (quin, 2H), 3.34 (s, 3H), 3.43 - 3.55 (m, 2H), 4.18 (t, 2H), 4.56 (q, 1H), 4.64 (t, 2H), 6.78 (s, 1H), 7.09 (s, 1H), 7.26 (s, 1H), 7.32 (d, 1H), 8.06 (d, 1H), 8.22 (s, 1H), 8.27 (s, 1H), 8.34 (s, 1H), 8.36 (s, 1H), 9.60 (s, 1H)
50g*		468 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 6H), 2.32 (quin, 2H), 4.17 (t, 2H), 4.29 (t, 2H), 4.57 (quin, 1H), 6.87 (s, 1H), 7.20 (s, 1H), 7.29 (s, 1H), 8.10 (s, 1H), 8.19 (s, 1H), 8.21 (s, 1H), 8.32 (s, 1H), 8.42 (s, 1H), 9.62 (s, 1H)
50h		498 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 3H), 2.32 (quin, 2H), 3.35 (s, 3H), 3.43 - 3.57 (m, 2H), 4.17 (t, 2H), 4.29 (t, 2H), 4.57 (q, 1H), 6.93 (s, 1H), 7.24 (s, 1H), 7.35 (s, 1H), 8.10 (s, 1H), 8.19 (s, 1H), 8.21 (s, 1H), 8.32 (s, 1H), 8.42 (s, 1H), 9.62 (s, 1H)

* The isolated sample was contaminated with approximately 15% of an unknown impurity following initial chromatography.

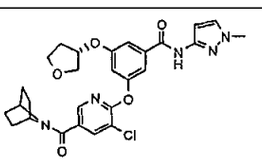
The preparations of 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid, 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid, 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid, 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]benzoic acid, and 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}benzoic acid were described earlier.

Example 51: 3-{[3-Chloro-5-(morpholin-4-ylcarbonyl)pyridin-2-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (152 mg, 0.5 mmol) and 4-[(5,6-dichloropyridin-3-yl)carbonyl]morpholine (143 mg, 0.55 mmol) in acetonitrile (5 mL) and the mixture heated at 120°C in a microwave reactor for 2 hours. The acetonitrile was evaporated *in vacuo* and the residue partitioned between water (25 mL) and ethyl acetate (50 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired compound (203 mg). ^{1}H NMR δ ($CDCl_3$): 2.05 – 2.2 (m, 2H), 3.4 – 3.7 (m, 8H), 3.7 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.9 (m, 1H), 6.7 (d, 1H), 6.8 (d, 1H), 7.15 (d, 1H), 7.25 (d, 2H), 7.85 (d, 1H), 8.0 (d, 1H), 8.95 (s, 1H); *m/z* 512 $(M+H)^+$.

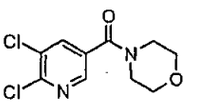
The following compound was prepared in an analogous fashion from 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide and 7-[(5,6-dichloropyridin-3-yl)carbonyl]-7-azabicyclo[2.2.1]heptane

Example	Structure	m/z	NMR
51a		538 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.5 (m, 4H), 1.7 – 1.9 (m, 4H), 2.05 – 2.2 (m, 2H), 3.7 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.1 (m, 1H), 4.7 (m, 1H), 4.9 (m, 1H), 6.75 (d, 1H), 6.85 (d, 1H), 7.2 (d, 1H), 7.25 (d, 2H), 8.0 (d, 1H), 8.2 (d, 1H) and 9.0 (s, 1H).

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide was described earlier.

The preparation of 4-[(5,6-dichloropyridin-3-yl)carbonyl]morpholine is described below:

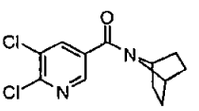
4-[(5,6-Dichloropyridin-3-yl)carbonyl]morpholine



Oxalyl chloride (3.2 mL; 36.0 mmol) was added to a solution of 5,6 dichloronicotinic acid (5.76 g; 30.0 mmol) and 4M hydrogen chloride in dioxane (7.5 mL; 30 mmol) in DCM (50 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*, the residue azeotroped with toluene (2 x 15 mL) and added to a solution of morpholine (3.1 mL; 36.0 mmol) and triethylamine (10.0 mL; 72 mmol) in DCM (150 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*, and the residue partitioned between water (75 mL) and ethyl acetate (100 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in isohexane, to give the desired compound (7.1 g).
^{1}H NMR δ ($CDCl_3$): 3.3 – 3.8 (br, 8H), 7.8 (s, 1H), 8.25 (s, 1H); *m/z* 261 $(M+H)^+$.

The preparation of 7-[(5,6-dichloropyridin-3-yl)carbonyl]-7-azabicyclo[2.2.1]heptane is described below:

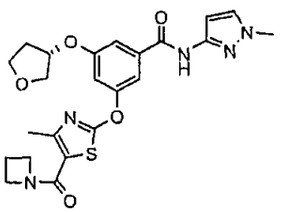
7-[(5,6-Dichloropyridin-3-yl)carbonyl]-7-azabicyclo[2.2.1]heptane



Oxalyl chloride (3.2 mL; 36.0 mmol) was added to a solution of 5,6 dichloronicotinic acid (5.76 g, 30.0 mmol) and 4M hydrogen chloride in dioxane (7.5 mL; 30.0 mmol) in DCM (50 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo*, the residue azeotroped with toluene (2 x 15 mL) and added to a solution of 7-azabicyclo[2.2.1]heptane hydrochloride (4.75 g; 36.0 mmol) and triethylamine (15.1 mL; 108 mmol) in DCM (150 mL). The mixture was stirred at RT for 18 hours, the DCM evaporated *in vacuo* and the residue partitioned between water (75 mL) and ethyl acetate

(150 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give a solid which was crystallised from ethyl acetate to give the desired compound (5.45 g). ^{1}H NMR δ ($CDCl_3$): 1.5 (m, 4H), 1.85 (m, 4H), 4.0 (br, 1H), 4.65 (br, 1H), 7.9 (s, 1H), 8.4 (s, 1H); *m/z* 271 $(M+H)^+$.

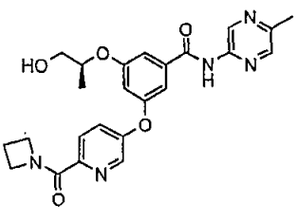
Example 52: 3-{[5-(Azetidin-1-ylcarbonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



Cesium carbonate (489 mg, 1.5 mmol) was added to a solution of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (152 mg, 0.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2-bromo-4-methyl-1,3-thiazole (144 mg, 0.55 mmol) in acetonitrile (5 mL) and the stirred mixture heated at 120°C in a microwave reactor for 2 hours. The mixture was allowed to cool, the acetonitrile evaporated *in vacuo*, and the residue partitioned between water (25 mL) and ethyl acetate (50 mL). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired compound as a solid which was further crystallised from an ethyl acetate / isohexane mixture (122 mg). ^{1}H NMR δ ($CDCl_3$): 2.0 – 2.15 (m, 2H), 2.2 – 2.3 (m, 2H), 2.5 (s, 3H), 3.75 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.1 – 4.3 (m, 4H), 4.9 (m, 1H), 6.75 (d, 1H), 6.95 (d, 1H), 7.25 (d, 2H), 7.3 (d, 1H) and 8.8 (s, 1H); *m/z* 484 $(M+H)^+$.

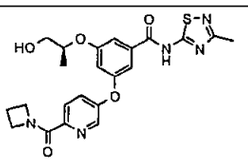
The preparations of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide and 5-(azetidin-1-ylcarbonyl)-2-bromo-4-methyl-1,3-thiazole were described earlier.

Example 53: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide



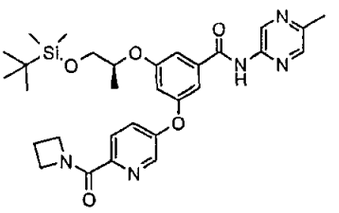
1M Hydrochloric acid (5 mL) was added to a solution of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (82 mg, 0.14 mmol) in methanol (5 mL) and stirred at RT for 1 hour. The methanol was removed *in vacuo* and the residue taken to pH6, extracted into ethyl acetate (3 x 50 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$), filtered and reduced *in vacuo*. The crude yellow oil was chromatographed on silica, eluting with 0-5% methanol in ethyl acetate, to give the desired compound as a white foam (36 mg). The compound could be crystallised from a mixture of *tert*-butylmethyl ether and methanol. ^{1}H NMR δ ($CDCl_3$): 1.24 (d, 3H), 1.81 (s, 1H), 2.28 (quin, 2H), 2.48 (s, 3H), 3.67 - 3.72 (m, 2H), 4.17 (t, 2H), 4.47 - 4.54 (m, 1H), 4.63 (t, 2H), 6.73 (t, 1H), 7.09 (t, 1H), 7.25 (t, 1H), 7.27 - 7.30 (m, 1H), 8.01 - 8.06 (m, 2H), 8.24 (d, 1H), 8.58 (s, 1H), 9.44 (d, 1H); *m/z* 464 $(M+H)^+$

The following compound was synthesised in an analogous fashion from 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide.

Example	Structure	m/z	NMR
53a		470 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.22 (d, 3H), 2.28 (quin, 2H), 2.40 (s, 3H), 3.00 (s, 1H), 3.70 (d, 2H), 4.16 (t, 2H), 4.51 (sextet, 1H), 4.64 (t, 2H), 6.74 (t, 1H), 7.20 - 7.27 (m, 3H), 7.97 (d, 1H), 8.23 (d, 1H), 11.55 (s, 1H)

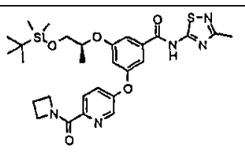
The preparation of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide is described below.

3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.11 mL, 0.80 mmol) was added to a solution of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid (0.3 g, 0.62 mmol) in DCM (10 mL) and stirred for 1 hour. 2-Amino-5-methylpyrazine (135 mg, 1.23 mmol), then pyridine (0.1 mL, 1.23 mmol), were added and the mixture stirred for a further 30 mins before being reduced *in vacuo* and partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was further extracted into ethyl acetate (50 mL) and the combined organics washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and reduced *in vacuo*. The crude oil was chromatographed on silica, eluting with 40-100% ethyl acetate in isohexane, to give the desired compound as a colourless oil (82 mg). ^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.28 (d, 3H), 2.32 (quin, 2H), 2.53 (s, 3H), 3.64 - 3.77 (m, 2H), 4.22 (t, 2H), 4.47 - 4.51 (m, 1H), 4.68 (t, 2H), 6.81 (t, 1H), 7.10 (t, 1H), 7.27 (t, 1H), 7.33 - 7.35 (m, 1H), 8.08 - 8.11 (m, 2H), 8.30 (d, 1H), 8.37 (s, 1H), 9.50 (d, 1H); *m/z* 578 $(M+H)^+$

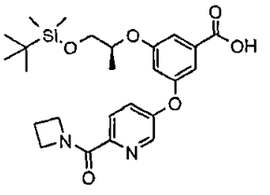
3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide was prepared in an analogous fashion from 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid.

Structure	m/z
	584 $(M+H)^+$

The preparation of 2-amino-5-methylpyrazine was described earlier.

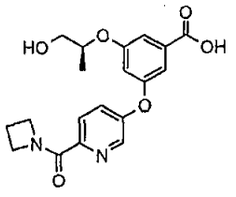
The preparation of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid is described below.

3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid



tert-Butyldimethylsilyl chloride (1.11 g, 7.36 mmol) was added to a mixture of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}benzoic acid (1.37g, 3.68 mmol) and 1,8-diazabicyclo(5,4,0)undec-7-ene (1.11 mL, 7.36 mmol) in acetonitrile (20 mL) and stirred at RT for 24 hours. The solvent was removed *in vacuo* and water (80 mL) added to the resultant oil. The mixture was adjusted to pH 10 with 1M sodium bicarbonate solution then washed with ether (80 mL) to remove impurities. The aqueous layer was adjusted to pH 3 with 1M citric acid and extracted into ethyl acetate (2 x 100 mL) and the combined organics washed with brine (50 mL), dried ($MgSO_4$), filtered and reduced *in vacuo*. The crude material was chromatographed on an Isolute NH2 cartridge, eluting with methanol then ammonia in methanol, to give a beige foam. This material was subsequently triturated with ethyl acetate to give the desired compound as a beige foam (1.0 g). ^{1}H NMR δ ($CDCl_3$): 0.01 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.27 (d, 3H), 2.26 - 2.35 (m, 2H), 3.58 - 3.79 (m, 2H), 4.15 - 4.25 (m, 2H), 4.43 - 4.49 (m, 1H), 4.60 - 4.69 (m, 2H), 6.77 - 6.82 (m, 1H), 7.28 (m, 2H), 7.42 - 7.44 (m, 1H), 8.02 - 8.07 (m, 1H), 8.27 - 8.29 (m, 1H); *m/z* 487 $(M+H)^+$

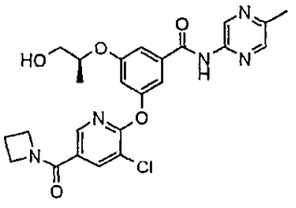
3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}benzoic acid



A mixture of methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate (2.35 g, 10.39 mmol), 2-(azetidin-1-ylcarbonyl)-5-bromopyridine (2.51 g, 10.39 mmol), cesium carbonate (10.16 g, 31.16 mmol) and bromotris(triphenylphosphine)copper (1.93 g, 2.08 mmol) in DMA (20 mL) was stirred in a microwave reactor at 160°C for 8 hours. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was acidified with 1M citric acid and extracted into ethyl acetate (2 x 100 mL), washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude oil was chromatographed on an Isolute NH2 cartridge, eluting with methanol then ammonia in methanol, to give the desired material as a beige foam (1.37 g). *m/z* 373 $(M+H)^+$

The preparations of methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate and 2-(azetidin-1-ylcarbonyl)-5-bromopyridine were described earlier.

Example 54: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide

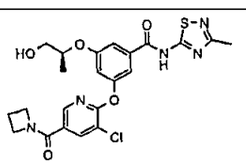
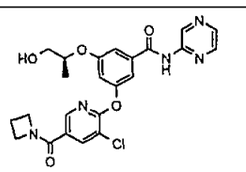
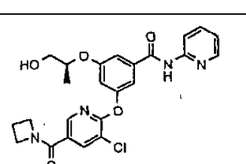


1M Hydrochloric acid (10 mL) was added to a solution of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (180 mg, 0.29 mmol) in methanol (10 mL) and stirred at RT for 1 hour. The methanol was removed *in vacuo* and the residue adjusted to pH 6 then extracted into ethyl acetate (3 x 50 mL). The combined organics

were washed with brine (50 mL), dried ($MgSO_4$), and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with 0-5% methanol in ethyl acetate, to give the desired compound as a white foam (134 mg). The compound was crystallised from ethyl acetate and methanol.

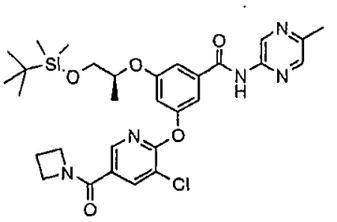
^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.40 (quin, 2H), 2.56 (s, 3H), 3.76 - 3.81 (m, 2H), 4.25 (t, 2H), 4.38 (t, 2H), 4.57 - 4.64 (m, 1H), 6.98 (t, 1H), 7.31 (t, 1H), 7.42 (t, 1H), 8.14 (s, 1H), 8.17 (d, 1H), 8.26 (d, 1H), 8.64 (s, 1H), 9.55 (s, 1H); *m/z* 498 $(M+H)^+$

The following compounds were prepared in an analogous fashion:

Example	Structure	m/z	NMR
54a		504 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.30 (d, 3H), 2.40 (quin, 2H), 2.47 (s, 3H), 3.23 (s, 1H), 3.78 - 3.79 (m, 2H), 4.25 (t, 2H), 4.38 (t, 2H), 4.58 (sextet, 1H), 6.97 (t, 1H), 7.39 - 7.40 (m, 2H), 8.15 (d, 1H), 8.22 (d, 1H), 11.68 (s, 1H)
54b		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.02 (t, 1H), 2.33 (quin, 2H), 3.70 - 3.73 (m, 2H), 4.17 (t, 2H), 4.30 (t, 2H), 4.52 - 4.56 (m, 1H), 6.93 (t, 1H), 7.24 (t, 1H), 7.35 (t, 1H), 8.10 (d, 1H), 8.19 (d, 1H), 8.21 - 8.22 (m, 1H), 8.33 (d, 1H), 8.43 (s, 1H), 9.61 (d, 1H)
54c		483 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.17 (t, 1H), 2.32 (quin, 2H), 3.67 - 3.74 (m, 2H), 4.17 (t, 2H), 4.30 (t, 2H), 4.49 - 4.56 (m, 1H), 6.89 (t, 1H), 7.00 - 7.03 (m, 1H), 7.23 (t, 1H), 7.34 (t, 1H), 7.67 - 7.71 (m, 1H), 8.10 (d, 1H), 8.18 (d, 1H), 8.22 - 8.23 (m, 1H), 8.28 (d, 1H), 8.54 (s, 1H)

The preparation of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide is described below.

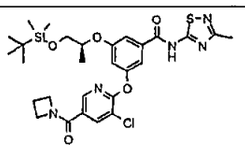
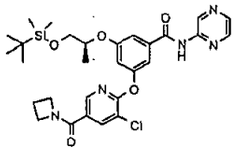
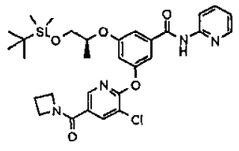
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.1 mL, 0.75 mmol) was added to a solution of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid (0.3 g, 0.58 mmol) in DCM (10 mL) and stirred for 1 hour. 2-Amino-5-methylpyrazine (126 mg, 1.15 mmol) then pyridine (0.094 mL, 1.15 mmol) were added and the mixture stirred for a further 30 mins before being reduced *in vacuo* and partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was further extracted into ethyl acetate (50 mL) and the combined organics washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), and reduced *in vacuo*. The crude oil was chromatographed on silica, eluting with 40-100% ethyl acetate in isohexane, to give the title compound as an oil (180 mg).

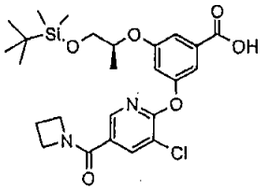
^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.82 (s, 9H), 1.28 (d, 3H), 2.35 (quin, 2H), 2.51 (s, 3H), 3.63 - 3.78 (m, 2H), 4.19 (t, 2H), 4.32 (t, 2H), 4.47 - 4.51 (m, 1H), 6.95 (t, 1H), 7.23 - 7.24 (m, 1H), 7.35 (t, 1H), 8.08 (s, 1H), 8.12 (d, 1H), 8.21 (d, 1H), 8.45 (s, 1H), 9.51 (d, 1H); *m/z* 612 $(M+H)^+$

The following intermediates used in the preparation of **Examples 54a-c** were prepared in an analogous fashion.

Structure	m/z	NMR
	618 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.37 (d, 3H), 2.30 - 2.38 (m, 5H), 3.61 - 3.79 (m, 2H), 4.19 (t, 2H), 4.30 (t, 2H), 4.41 - 4.47 (m, 1H), 6.84 - 6.86 (m, 1H), 7.62 - 7.62 (m, 1H), 7.72 - 7.73 (m, 1H), 8.10 - 8.11 (m, 1H), 8.19 - 8.20 (m, 1H), 9.89 (s, 1H)
	598 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.29 (d, 3H), 2.35 (quin, 2H), 3.64 - 3.79 (m, 2H), 4.19 (t, 2H), 4.32 (t, 2H), 4.47 - 4.51 (m, 1H), 6.96 (s, 1H), 7.25 (s, 1H), 7.36 (s, 1H), 8.12 (d, 1H), 8.21 (d, 1H), 8.23 (s, 1H), 8.34 (d, 1H), 8.52 (s, 1H), 9.64 (s, 1H)
	597 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.28 (d, 3H), 2.35 (quin, 2H), 3.63 - 3.78 (m, 2H), 4.19 (t, 2H), 4.32 (t, 2H), 4.46 - 4.50 (m, 1H), 6.93 (t, 1H), 7.01 - 7.05 (m, 1H), 7.23 - 7.23 (m, 1H), 7.34 (t, 1H), 7.69 - 7.73 (m, 1H), 8.12 (d, 1H), 8.21 (d, 1H), 8.24 (d, 1H), 8.31 (d, 1H), 8.56 (s, 1H)

The preparation of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid is described below.

3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]benzoic acid

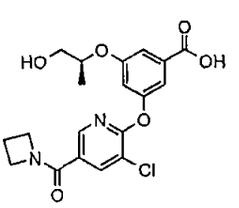


tert-Butyldimethylsilyl chloride (2.78 g, 18.4 mmol) was added to a mixture of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}benzoic acid (3.74 g, 9.19 mmol) and 1,8-diazabicyclo(5,4,0)undec-7-ene (2.75 mL, 7.36 mmol) in acetonitrile (40 mL) and stirred at RT for 24 hours. The solvent

was removed *in vacuo* and water (80 mL) added to the resultant oil. The mixture was adjusted to pH 10 with 1M sodium bicarbonate solution and washed with ether to remove any impurities. The aqueous layer was adjusted to pH 3 with 1M citric acid and extracted into ethyl acetate (2 x 100 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give the desired compound as a white foam (2.9 g).

^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.28 (d, 3H), 2.35 (quin, 2H), 3.62 - 3.78 (m, 2H), 4.21 (t, 1H), 4.32 (t, 1H), 4.43 - 4.50 (m, 1H), 6.95 - 6.98 (m, 1H), 7.42 - 7.45 (m, 1H), 7.50 - 7.53 (m, 1H), 8.12 (d, 1H), 8.22 (d, 1H); *m/z* 521 $(M+H)^+$

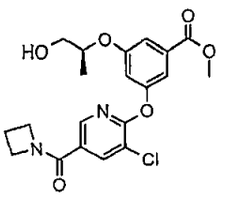
3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}benzoic acid



Lithium hydroxide monohydrate (529 mg, 12.59 mmol) in water (25 mL) was added to a solution of methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}benzoate (5.3 g, 12.6 mmol) in THF (50 mL) and stirred at RT for 3 hours. The THF was removed *in vacuo* and the aqueous layer was washed with ethyl acetate (50 mL) to remove any impurities. The aqueous layer was acidified and extracted into ethyl acetate (2 x 50 mL), and the organics washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the desired compound as a white foam (3.74 g).

^{1}H NMR δ ($CDCl_3$): 1.24 (d, 3H), 2.31 (quin, 2H), 3.65 - 3.72 (m, 2H), 4.17 (t, 2H), 4.29 (t, 2H), 4.47 - 4.54 (m, 1H), 6.93 (t, 1H), 7.40 (s, 1H), 7.46 (s, 1H), 8.08 (d, 1H), 8.19 (d, 1H); *m/z* 407 $(M+H)^+$

Methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}benzoate

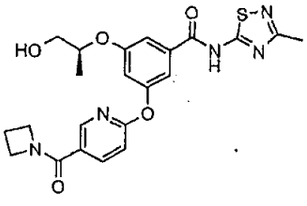


A mixture of methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate (2.35 g, 10.39 mmol), 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (2.41 g, 10.39 mmol) and potassium carbonate (2.87 g, 20.8 mmol) in acetonitrile (20 mL) was stirred in a microwave reactor at 160°C for 6 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. The crude oil was chromatographed on silica, eluting with 30-100% ethyl acetate in isohexane, to give the desired compound as a yellow oil (5.3 g).

^{1}H NMR δ ($CDCl_3$): 1.24 (d, 3H), 1.94 (t, 1H), 2.32 (quin, 2H), 3.65 - 3.72 (m, 2H), 3.83 (s, 3H), 4.16 (t, 2H), 4.28 (t, 2H), 4.47 - 4.54 (m, 1H), 6.90 (t, 1H), 7.37 - 7.38 (m, 1H), 7.43 - 7.45 (m, 1H), 8.08 (d, 1H), 8.18 (d, 1H); *m/z* 421 $(M+H)^+$

The preparations of methyl 3-hydroxy-5-[(1*S*)-2-hydroxy-1-methylethoxy]benzoate and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine were described earlier.

Example 55: 3-{[5-(Azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide

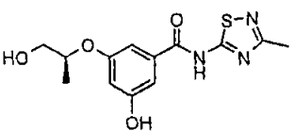


A mixture of 3-hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide (237 mg, 0.77 mmol), 5-(azetidin-1-ylcarbonyl)-2-chloropyridine (151 mg, 0.77 mmol) and potassium carbonate (213 mg, 1.54 mmol) in

acetonitrile (5 mL) was stirred in a microwave reactor at 140°C for 5 hours and at 160°C for 10 hours. The mixture was reduced *in vacuo* and ethyl acetate (50 mL) added. The mixture was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), and reduced *in vacuo* to give a brown oil which was chromatographed on silica, eluting with 0-10% methanol in ethyl acetate, to give the desired compound as a white foam (64 mg). ^1H NMR δ ($CDCl_3$): 1.29 (d, 3H), 2.38 (quin, 2H), 2.49 (s, 3H), 2.72 (s, 1H), 3.75 - 3.77 (m, 2H), 4.20 - 4.41 (m, 4H), 4.51 - 4.59 (m, 1H), 6.95 (t, 1H), 6.99 (d, 1H), 7.35 (t, 1H), 7.37 - 7.38 (m, 1H), 8.05 - 8.08 (m, 1H), 8.40 (d, 1H), 11.08 (s, 1H); *m/z* 470 $(M+H)^+$

The preparation of 5-(azetidin-1-ylcarbonyl)-2-chloropyridine was described earlier.
The preparation of 3-hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide is described below.

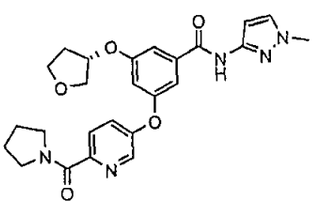
3-Hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide



Iodotrimethylsilane (5.51 mL, 38.7 mmol) was added to 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide (2.5 g, 7.73 mmol) in acetonitrile (25 mL) and the reaction stirred at RT for 48 hours. Methanol (15 mL) was added and the reaction stirred for 1 hour then a saturated solution of sodium thiosulphate (10 mL) was added and stirred for 20 mins. The volatiles were removed *in vacuo* and the aqueous residue extracted into ethyl acetate (2 x 150 mL). The organics were washed with water, brine, dried ($MgSO_4$), and reduced *in vacuo* to give a yellow solid. The solid was triturated with DCM and then with ethyl acetate to give the desired compound as a white solid (1.44 g). ^1H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.49 (s, 3H), 3.46 - 3.59 (m, 2H), 4.48 - 4.52 (m, 1H), 4.89 (t, 1H), 6.60 (s, 1H), 7.08 (s, 1H), 7.24 (s, 1H), 9.91 (s, 1H), 13.28 (s, 1H); *m/z* 310 $(M+H)^+$

The preparation of 3-hydroxy-5-{[(1*S*)-2-methoxy-(1-methylethyl)oxy}-*N*-(3-methyl-1,2,4-thiadiazol-2-yl)benzamide was described earlier.

Example 56: *N*-(1-methyl-1*H*-pyrazol-3-yl)-3-{[6-(pyrrolidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



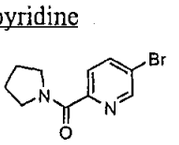
Copper (I) iodide (95 mg, 0.5 mmol), 2,2,6,6-tetramethyl-3,5-heptanedione (0.42 mL, 2.0 mmol) and cesium carbonate (489 mg, 1.5 mmol) were added to a solution of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide (152 mg, 0.5 mmol) and 5-bromo-2-(pyrrolidin-1-ylcarbonyl)pyridine (141 mg, 0.55 mmol) in NMP (5 mL) and the stirred mixture heated at 160°C in a microwave reactor for 12 hours. The mixture was cooled to RT and pressure, the mixture partitioned between water (75 mL) and ethyl acetate (50 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with ethyl acetate, to give the desired material (81 mg).

^{1}H NMR δ ($CDCl_3$): 1.8 – 1.95 (m, 4H), 2.0 – 2.2 (m, 2H), 3.6 (m, 2H), 3.75 (s, 3H), 3.85 (m, 2H), 3.95 (m, 2H), 4.9 (m, 1H), 6.65 (m, 1H), 6.75 (m, 1H), 7.1 (m, 1H), 7.2 (s, 1H), 7.25 (m, 1H), 7.3 (dd, 1H), 7.8 (d, 1H), 8.25 (d, 1H), 8.8 (s, 1H); *m/z* 478 $(M+H)^+$.

The preparation of 3-hydroxy-*N*-(1-methyl-1*H*-pyrazol-3-yl)-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide was described earlier.

The preparation of 5-bromo-2-(pyrrolidin-1-ylcarbonyl)pyridine is described below.

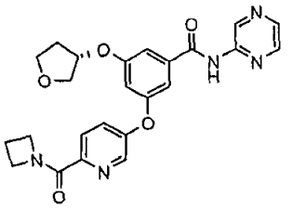
5-Bromo-2-(pyrrolidin-1-ylcarbonyl)pyridine



Oxalyl chloride (0.83 mL; 9.3 mmol) and DMF (1 drop) were added to a solution of 5-bromoisonicotinic acid (1.57 g; 7.75 mmol) and 4M hydrogen chloride in dioxan (1.93 mL; 7.75 mmol) in DCM (50 mL). The mixture was stirred at RT for 18 hours, the DCM removed *in vacuo* and the residue azeotroped with toluene (2 x 15 mL). The residue was

and added to a solution of pyrrolidine (0.78 mL; 9.3 mmol) and triethylamine (2.6 mL; 18.6 mmol) in DCM (40 mL) and the mixture stirred at RT for 6 hours. The DCM was removed *in vacuo*, the residue partitioned between water (75 mL) and ethyl acetate (100 mL), the organic layer washed with brine, dried ($MgSO_4$) and evaporated to a residue which was chromatographed on silica, eluting with 50% ethyl acetate in *iso* hexane, to give the desired material (1.40 g). ^{1}H NMR δ ($CDCl_3$): 1.85 (m, 4H), 3.6 (m, 2H), 3.7 (s, 3H), 7.7 (d, 1H), 7.85 (s, 1H), 8.55 (s, 1H); *m/z* 257 $(M+H)^+$.

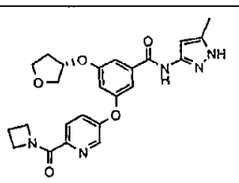
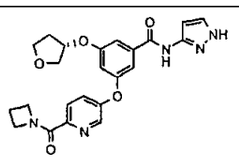
Example 57: 3-{[6-(Azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-*N*-pyrazin-2-yl-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzamide



1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.095 mL, 0.75 mmol) was added to a solution of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid (250 mg, 0.65 mmol) in DCM (6 mL) and stirred at RT for 30 - 40 minutes. 2-Aminopyrazine (125 mg, 1.31 mmol) and pyridine (0.106 mL, 1.31 mmol) were added and the reaction stirred at RT for 2 hours. The solvent was removed *in vacuo*, water (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined and washed with 2N hydrochloric acid (20 mL), a saturated solution of sodium bicarbonate (20 mL), water (20 mL), brine (20 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was chromatographed on silica, eluting with a gradient of 0-10% methanol in DCM, to give the desired compound (71 mg). ^{1}H NMR δ ($CDCl_3$): 2.13 - 2.30 (m, 2H), 2.32 - 2.39 (m, 2H), 3.89 - 4.04 (m, 4H), 4.25 (t, 2H), 4.71 (t, 2H), 4.97 - 5.01 (m, 1H), 6.77 (t, 1H), 7.16 (t, 1H), 7.25 (s, 1H), 7.40 (dd, 1H), 8.14 (d, 1H), 8.28 (dd, 1H), 8.34 (d, 1H), 8.38 (s, 1H), 8.40 (d, 1H), 9.66 (d, 1H); *m/z* 462 $(M+H)^+$, 460 $(M-H)^-$

The following compounds were prepared in an analogous fashion from 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid and either 1,1-

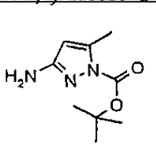
dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate or 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate. The material produced was dissolved in acetonitrile (3mL) and heated at 150°C in a microwave reactor for 10 minutes to give the desired material after chromatography.

Example	Structure	m/z	NMR
57a		464 $(M+H)^+$ 462 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.27 (2H, m), 2.31 - 2.39, (2H, m), 2.33 (3H, s), 3.87 - 4.01 (4H, m), 4.24 (2H, t), 4.70 (2H, t), 4.95 - 4.98 (1H, m), 6.57 (1H, s), 6.73 (1H, t), 7.13 (1H, t), 7.24 (1H, t), 7.35 - 7.38 (1H, m), 8.10 (1H, d), 8.31 (1H, d), 8.79 (1H, s)
57b		450 $(M+H)^+$ 448 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.11 - 2.27 (2H, m), 2.30 - 2.38 (2H, m), 3.87 - 4.02 (4H, m), 4.22 (2H, t), 4.69 (2H, t), 4.95 - 4.97 (1H, m), 6.74 (1H, t), 6.77 (1H, s), 7.19 (1H, s), 7.30 (1H, s), 7.32 - 7.35 (1H, m), 7.51 (1H, d), 8.06 (1H, d), 8.30 (1H, d), 9.59 (1H, s)

The preparations of 3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3*S*)-tetrahydrofuran-3-yloxy]benzoic acid and 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate were described earlier.

The preparation of 1,1-dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate is described below.

1,1-Dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate

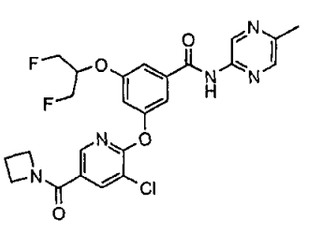


5-Methyl-1*H*-pyrazol-3-amine (800 mg, 8.25 mmol) was dissolved in DMF (10 mL) at 0 °C and treated with sodium hydride (336 mg, 8.25 mmol) followed by stirring for a further 30 minutes. Warmed di-*tert*-butyl dicarbonate (1.80 g, 8.25 mmol) was then slowly added via syringe over 5 min and the reaction was allowed to warm to RT and stirred for a further

1 hour. The reaction was taken up in saturated aqueous sodium hydrogencarbonate (50 mL) and ethyl acetate (100 mL). The organic layer was separated then dried ($MgSO_4$), filtered and evaporated. Purification by column chromatography, eluting with 50-100% ethyl acetate in isohexane, afforded the title compound as a colourless oil (380 mg).

^{1}H NMR δ ($CDCl_3$): 1.62 (s, 9H), 2.43 (s, 3H), 3.87 (br. s, 2H), 5.60 (s, 1H)

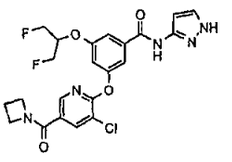
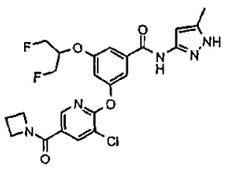
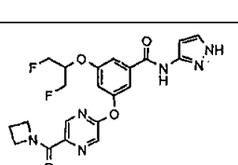
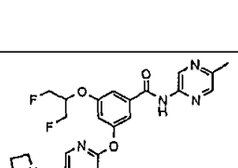
Example 58: 3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide



1-Chloro-*N,N*-2-trimethylpropenylamine (0.08 mL, 0.60 mmol) was added to a solution of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoic acid (215 mg, 0.5 mmol) in DCM (5 mL) and the reaction stirred at RT for 30 - 40 minutes. Pyridine (0.08 mL, 1.0 mmol) and 2-amino-5-methylpyrazine (108 mg, 1.0 mmol) were added and the reaction stirred for 16 hours before being concentrated *in vacuo* and water (20 mL) added. The mixture was extracted with ethyl acetate (3 x 20 mL), washed with 1N hydrochloric acid (20 mL), a saturated solution of sodium hydrogen carbonate (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed on silica, eluting with a gradient of 0-10% methanol in DCM, to give the desired compound as a white solid (150 mg). ^{1}H NMR δ ($CDCl_3$): 2.40 (quintet, 2H), 2.56 (s, 3H), 4.22-4.31 (m, 2H), 4.32-4.40 (m, 2H), 4.62 - 4.82 (m, 5H), 7.06 (t, 1H), 7.38 (t, 1H), 7.47 (t, 1H), 8.15 (s, 1H), 8.17 (s, 1H), 8.25 (d, 1H), 8.46 (s, 1H), 9.55 (s, 1H); *m/z* 518 $(M+H)^+$, 516 $(M-H)^-$

The following compounds were prepared in an analogous fashion from the appropriate benzoic acid and either 2-amino-5-methylpyrazine, 1,1-dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate or 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate. In the instances where either 1,1-dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate or 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate were used, an additional step was

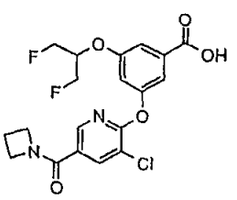
required to obtain the desired material. This additional step required the material to be dissolved in acetonitrile (3mL) and heated at 150°C in a microwave reactor for 10 minutes, the desired material was then isolated after chromatography.

Example	Structure	m/z	NMR
58a		492 $(M+H)^+$ 490 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.39 (quin, 2H), 4.22 (t, 2H), 4.33 (t, 2H), 4.59 - 4.81 (m, 5H), 6.86 (s, 1H), 6.99 (s, 1H), 7.37 (s, 1H), 7.41 (s, 2H), 8.16 (d, 1H), 8.19 (d, 1H), 10.32 (s, 1H)
58b		506 $(M+H)^+$ 504 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.24 (s, 3H), 2.38 (quin, 2H), 4.23 (t, 2H), 4.34 (t, 2H), 4.59 - 4.79 (m, 5H), 6.59 (s, 1H), 7.00 (t, 1H), 7.34 (s, 1H), 7.37 (s, 1H), 8.16 (d, 1H), 8.19 (d, 1H), 9.95 (s, 1H)
58c		459 $(M+H)^+$ 457 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 2.25-2.35 (m, 2H), 4.12 - 4.18 (m, 2H), 4.50 - 4.70 (m, 7H), 6.65 (s, 1H), 6.9 (s, 1H), 7.35 (s, 1H), 7.37 (s, 1H), 7.45 (s, 1H), 8.25 (s, 1H), 8.70 (s, 1H), 10.60 (s, 1H)
58d		485 $(M+H)^+$ 483 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.34 - 2.42 (m, 2H), 2.58 (s, 3H), 4.26 (t, 2H), 4.69 (t, 2H), 4.63 – 4.81 (m, 5H), 7.05 (t, 1H), 7.37 (t, 1H), 7.45 - 7.46 (m, 1H), 8.14 (d, 1H), 8.34 (s, 1H), 8.37 (d, 1H), 8.86 (d, 1H), 9.53 (d, 1H)

The preparations of 1,1-dimethylethyl 3-amino-5-methyl-1*H*-pyrazole-1-carboxylate or 1,1-dimethylethyl 3-amino-1*H*-pyrazole-1-carboxylate were described earlier.

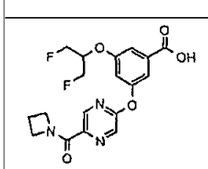
The preparation of 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoic acid is described below.

3-{[5-(Azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoic acid



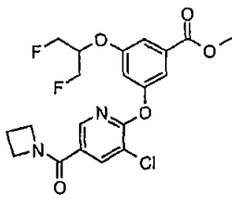
A mixture of methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoate (3.6 g, 8.2 mmol) in THF (50 mL) and water (50 mL) was treated with 1M sodium hydroxide solution (8.2 mL, 8.2 mmol) and allowed to stir at RT for 210 minutes. The THF was removed *in vacuo*, the residue filtered and extracted with ethyl acetate (30 mL). The aqueous layer was acidified with 2N hydrochloric acid, extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts washed with water (10 mL), brine (10 mL) and concentrated *in vacuo* to give the desired material as a pale yellow foam (2.84 g). ^{1}H NMR δ ($CDCl_3$): 2.36 - 2.44 (m, 2H), 4.26 (t, 2H), 4.37 (t, 2H), 4.62 - 4.79 (m, 5H), 7.08 (t, 1H), 7.56 - 7.57 (m, 1H), 7.58 - 7.59 (m, 1H), 8.17 (d, 1H), 8.27 (d, 1H); *m/z* 426 $(M+H)^+$, 424 $(M-H)^-$

3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoic acid was prepared in an analogous fashion from methyl 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoate

Structure	m/z	NMR
	394 $(M+H)^+$, 392 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 2.26 - 2.34 (m, 2H), 4.08 - 4.15 (m, 2H), 4.56 (t, 2H), 4.60 - 5.10 (m, 5H), 7.29 (t, 1H), 7.38 - 7.39 (m, 1H), 7.46 - 7.47 (m, 1H), 8.56 (d, 1H), 8.65 - 8.67 (m, 1H)

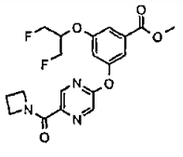
The preparation of methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoate is described below.

Methyl 3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoate



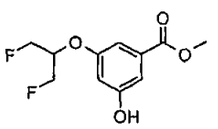
A solution of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzoate (1.78 g, 7.24 mmol), potassium carbonate (2.0 g, 14.5 mmol) and 5-(azetidin-1-ylcarbonyl)-2,3-dichloropyridine (2.08 g, 8.7 mmol) in acetonitrile (15mL) was heated in a microwave reactor at 130°C for 1 hour. The solution was diluted with ethyl acetate (150 mL), washed with water (3 x 50 mL), brine (20 mL), dried ($MgSO_4$), and the solvent removed *in vacuo* to give the desired material as an orange oil (3.6 g). ^{1}H NMR δ ($CDCl_3$): 2.35 - 2.44 (m, 2H), 3.91 (s, 3H), 4.24 – 4.27 (m, 2H), 4.34 - 4.37 (m, 2H), 4.62 - 4.81 (m, 5H), 7.04 (t, 1H), 7.51 (t, 1H), 7.55 (m, 1H), 8.15 (d, 1H), 8.25 (d, 1H); *m/z* 441 $(M+H)^+$

Methyl 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}benzoate was prepared in an analogous fashion from methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzoate.

Structure	m/z	NMR
	408 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.34 - 2.43 (m, 2H), 3.91 (s, 3H), 4.26 (t, 2H), 4.59 - 4.79 (m, 5H), 4.65 - 4.71 (m, 2H), 7.03 (t, 1H), 7.49 - 7.50 (m, 1H), 7.54 - 7.55 (m, 1H), 8.33 (d, 1H), 8.84 - 8.86 (m, 1H)

The preparation of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzoate is described below.

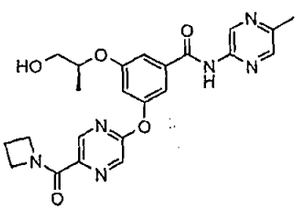
Methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-hydroxybenzoate



10% Palladium on charcoal (Pd/C; 50 mg) was added to a mixture of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate (1.2 g, 3.62 mmol) and ammonium formate (500 mg, 8.0 mmol) in ethanol (7 mL) and then heated at 140°C for 20 minutes in a microwave reactor. The reaction was repeated on the same scale and the two reaction mixtures combined, filtered and filtrate concentrated *in vacuo* to give the desired material as a pale yellow oil (2.1 g). ^{1}H NMR δ ($CDCl_3$): 3.82 (s, 3H), 4.58 - 4.77 (m, 5H), 6.72 (t, 1H), 7.17 - 7.22 (m, 2H); *m/z* 245 $(M-H)^-$

The preparation of methyl 3-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-5-[(phenylmethyl)oxy]benzoate was described earlier.

Example 59: 3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide

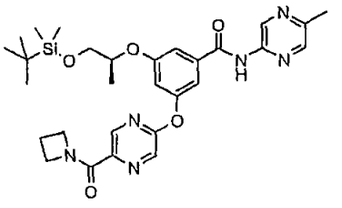


1M Hydrochloric acid (5 mL) was added to a solution of 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (90 mg, 0.16 mmol) in methanol (5 mL) and the mixture stirred at RT for 1 hour. The methanol was removed *in vacuo*, the residue adjusted to pH6 and then extracted into ethyl acetate (3 x 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), and reduced *in vacuo* to give a yellow oil which was chromatographed on silica, eluting with 0-5% methanol in ethyl acetate, to give the desired compound as a white foam (28 mg).

^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.11 (s, 1H), 2.38 (quin, 2H), 2.55 (s, 3H), 3.74 - 3.82 (m, 2H), 4.26 (t, 2H), 4.55 - 4.62 (m, 1H), 4.69 (t, 2H), 6.97 (t, 1H), 7.30 (t, 1H), 7.40 (t, 1H), 8.13 (s, 1H), 8.35 (d, 1H), 8.41 (s, 1H), 8.85 (d, 1H), 9.53 (d, 1H); *m/z* 465 $(M+H)^+$

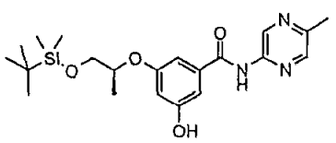
The preparation of 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide is described below.

3-{[5-(Azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



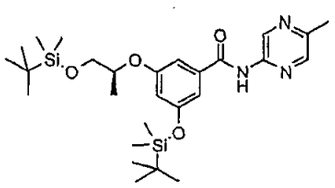
A mixture of 3-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-(5-methylpyrazin-2-yl)benzamide (0.12 g, 0.29 mmol), 2-(azetidin-1-ylcarbonyl)-5-chloropyrazine (57 mg, 0.29 mmol) and potassium carbonate (80 mg, 0.57 mmol) in acetonitrile (5 mL) was stirred in a microwave reactor at 140°C for 1 hour. The mixture was reduced *in vacuo* and ethyl acetate (50 mL) added. The mixture was washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and reduced *in vacuo* to give a brown oil which was chromatographed on silica, eluting with 50 to 100% ethyl acetate in isohexane, to give the desired compound as a colourless oil (90 mg). ^{1}H NMR δ ($CDCl_3$): -0.03 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.26 (d, 3H), 2.32 (quin, 2H), 2.49 (s, 3H), 3.61 - 3.76 (m, 2H), 4.20 (t, 2H), 4.46 (sextet, 1H), 4.62 (t, 2H), 6.91 (t, 1H), 7.21 (t, 1H), 7.32 (t, 1H), 8.07 (s, 1H), 8.28 (d, 1H), 8.30 (s, 1H), 8.79 (d, 1H), 9.48 (d, 1H). *m/z* 579 $(M+H)^+$

3-[((1*S*)-2-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-5-hydroxy-*N*-(5-methylpyrazin-2-yl)benzamide



Lithium hydroxide monohydrate (0.38 g, 9.12 mol) in water (20 mL) was added to a solution of 3-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide (1.94 g, 3.65 mol) in THF (40 mL) and stirred at RT for 20 hours. The THF was removed *in vacuo* and the aqueous layer was adjusted to pH7. Ethyl acetate (50 mL) and water (50 mL) were added then the aqueous layer re-extracted into ethyl acetate (50 mL) and the combined organics washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and reduced *in vacuo*. The crude material was chromatographed on silica, eluting with 20-50% ethyl acetate in isohexane, to give the desired material as a white solid (0.8 g). ^{1}H NMR δ ($CDCl_3$): 0.04 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.30 (d, 3H), 2.56 (s, 3H), 3.65 - 3.81 (m, 2H), 4.46 - 4.51 (m, 1H), 5.63 (s, 1H), 6.63 (t, 1H), 6.98 (t, 1H), 7.04 (t, 1H), 8.15 (s, 1H), 8.41 (s, 1H), 9.57 (s, 1H); *m/z* 418 $(M+H)^+$

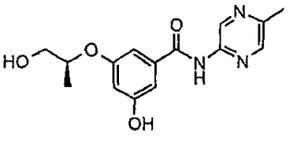
3-{[(1,1-Dimethylethyl)(dimethyl)silyl]oxy}-5-[((1*S*)-2-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-methylethyl)oxy]-*N*-(5-methylpyrazin-2-yl)benzamide



tert-Butyldimethylsilyl chloride (2.61 g, 17.31 mmol) was added to a solution of 3-hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide (1.5 g, 4.95 mmol) and imidazole (2.36 g, 34.62 mmol) in DMF (15 mL) and the reaction stirred at RT for 24 hours. Water was added and the product extraxted into ether (2 x 100 mL). The combined organics were washed with brine, dried ($MgSO_4$), filtered and reduced

in vacuo to give a yellow oil which was chromatographed on silica, eluting with 0-40% ethyl acetate in isohexane, to give the desired material as a colourless oil (1.94 g). ^{1}H NMR δ ($CDCl_3$): -0.03 (s, 3H), 0.01 (s, 3H), 0.16 (s, 6H), 0.81 (s, 9H), 0.92 (s, 9H), 1.23 (d, 3H), 2.48 (s, 3H), 3.58 - 3.74 (m, 2H), 4.37 - 4.42 (m, 1H), 6.54 (t, 1H), 6.86 (t, 1H), 6.99 (t, 1H), 8.06 (s, 1H), 8.21 (s, 1H), 9.48 (d, 1H).

3-Hydroxy-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide



Trimethylsilyl iodide (6.06 mL, 42.75 mmol) was added to a solution of 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide (2.71 g, 8.55 mmol) in dry acetonitrile (150 mL) and stirred for 24 hours. Methanol (30 mL) was added to quench the reaction and stirred for 10 minutes. 10% w/v Aqueous sodium thiosulfate pentahydrate (20 mL) was added to the mixture and the organic solvents removed *in vacuo*. The residue was brought to pH5 with 1M hydrochloric acid and ethyl acetate (80 mL) added. A yellow solid (1.4 g) was separated by filtration. The aqueous filtrate was reextracted into ethyl acetate (2x80 mL) and the combined organic layers dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. This residue was combined with the yellow solid obtained above and purified by column chromatography, eluting with 5% to 10% methanol in DCM, to give the title compound (1.70 g)

^{1}H NMR δ (d_6-DMSO): 1.21 (d, 3H), 2.50 (s, 3H), 3.40-3.60 (m, 2H), 4.45 (sex, 1H), 4.80 (t, 1H), 6.50 (s, 1H), 6.97 (s, 1H), 7.08 (s, 1H), 8.32 (s, 1H), 9.21 (s, 2H), 9.63 (s, 1H), 10.80 (brs, 1H). *m/z* 304 $(M+H)^+$

The preparation of 3-hydroxy-5-{[(1*S*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide was described earlier.

Example 59, 3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*S*)-2-hydroxy-1-methylethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide was also prepared in the following manner.

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3R)-tetrahydrofuran-3-yloxy]benzamide; and/or
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-isoxazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-pyrazin-2-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-(5-fluoropyridin-2-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyridin-2-ylbenzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-isoxazol-3-yl-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(4-methyl-1,3-thiazol-2-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methyl-1,3-thiazol-2-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyrazin-2-ylbenzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-pyrazin-2-ylbenzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyrazin-2-ylbenzamide;
3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-[(1-methylethyl)oxy]-N-pyrazin-2-ylbenzamide;
3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-pyrazin-2-ylbenzamide;
3-{[3-chloro-5-(morpholin-4-ylcarbonyl)pyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[5-(7-azabicyclo[2.2.1]hept-7-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide; and
3-{[5-(azetidin-1-ylcarbonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-N-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide; and/or

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-pyrazin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-pyridin-2-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyridin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(3-methyl-1,2,4-thiadiazol-5-yl)benzamide;

N-(1-methyl-1H-pyrazol-3-yl)-3-{[6-(pyrrolidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-pyrazin-2-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-(5-methyl-1H-pyrazol-3-yl)-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-1H-pyrazol-3-yl-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)-3-chloropyridin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(5-methyl-1H-pyrazol-3-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-1H-pyrazol-3-ylbenzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[2-fluoro-1-(fluoromethyl)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;

3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1S)-2-hydroxy-1-methylethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-({(1S)-2-[(difluoromethyl)oxy]-1-methylethyl}oxy)-N-1H-pyrazol-3-ylbenzamide;
3-{[5-(azetidin-1-ylsulfonyl)-4-methyl-1,3-thiazol-2-yl]oxy}-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}-N-(5-methylpyrazin-2-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-[1-(difluoromethyl)-1H-pyrazol-3-yl]-5-[(3S)-tetrahydrofuran-3-yloxy]benzamide;
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-N-[1-(difluoromethyl)-1H-pyrazol-3-yl]-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-N-[1-(difluoromethyl)-1H-pyrazol-3-yl]-5-{[(1S)-1-methyl-2-(methyloxy)ethyl]oxy}benzamide; and/or
3-{[5-(azetidin-1-ylcarbonyl)pyrazin-2-yl]oxy}-5-{[(1*R*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide;
3-{[6-(azetidin-1-ylcarbonyl)pyridin-3-yl]oxy}-5-{[(1*R*)-1-methyl-2-(methyloxy)ethyl]oxy}-*N*-(5-methylpyrazin-2-yl)benzamide;
or a salt thereof.

9. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 8, or a pharmaceutically-acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

10. A compound according to any one of Claims 1 to 8 or a pharmaceutically-acceptable salt thereof for use as a medicament.

11. A compound according to Claim 10, wherein the medicament is a medicament for treatment of a disease mediated through GLK, in particular type 2 diabetes.

12. The use of a compound according to any one of Claims 1 to 8, or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for treatment of a disease mediated through GLK.

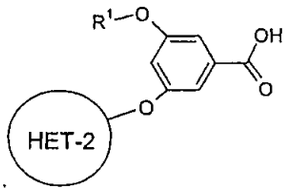
13. The use of a compound according to any one of Claims 1 to 8, or a pharmaceutically-acceptable salt thereof, in the preparation of a medicament for treatment of type 2 diabetes.

14. A method of treating GLK mediated diseases by administering an effective amount of a compound of Formula (I) or (IA) as claimed in any one of Claims 1 to 8 or a pharmaceutically-acceptable salt thereof, to a mammal in need of such treatment.

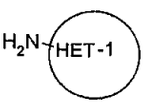
15. The method of Claim 14 wherein the GLK mediated disease is type 2 diabetes.

16. A process for the preparation of a compound of Formula (I) or (IA) as claimed in any one of Claims 1 to 8, which comprises a process a) to e) (wherein the variables are as defined for compounds of Formula (I) in Claim 1 unless otherwise stated):

(a) reaction of an acid of Formula (III) or activated derivative thereof with a compound of Formula (IV), wherein R^1 is as hereinbefore defined or a protected version thereof;



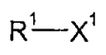
(III)



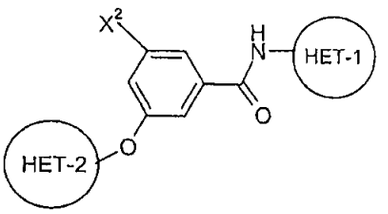
(IV);

or

(b) reaction of a compound of Formula (V) with a compound of Formula (VI),



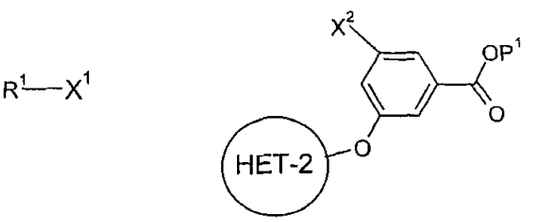
(V)



(VI)

wherein X^1 is a leaving group and X^2 is a hydroxyl group or X^1 is a hydroxyl group and X^2 is a leaving group, and wherein R^1 is as hereinbefore defined or a protected version thereof;

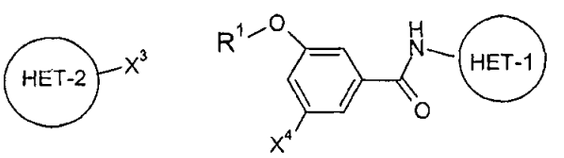
process (b) could also be accomplished using the intermediate ester Formula (VII), wherein P^1 is a protecting group as hereinafter described, followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;



(V) (VII)

or

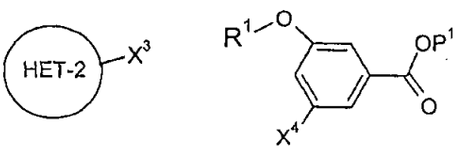
(c) reaction of a compound of Formula (VIII) with a compound of Formula (IX)



(VIII) (IX)

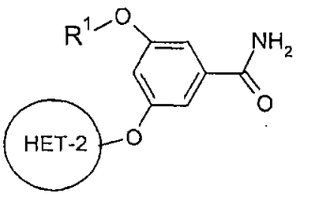
wherein X^3 is a leaving group or an organometallic reagent and X^4 is a hydroxyl group or X^3 is a hydroxyl group and X^4 is a leaving group or an organometallic reagent, and wherein R^1 is as hereinbefore defined or a protected version thereof;

process (c) could also be accomplished using the intermediate ester Formula (X), followed by ester hydrolysis and amide formation by procedures described elsewhere and well known to those skilled in the art;

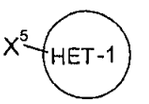


(VIII) (X)

(d) reaction of a compound of Formula (XI) with a compound of Formula (XII),



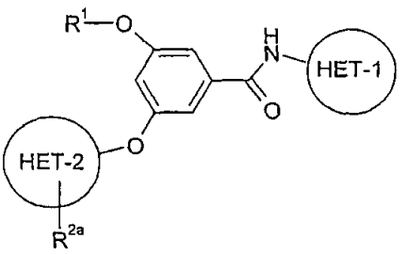
(XI)



(XII);

wherein X^5 is a leaving group; and wherein R^1 is as hereinbefore defined or a protected version thereof; or

e) reaction of a compound of formula (XIII)



(XIII)

wherein R^{2a} is a precursor to R^2, such as a carboxylic acid, ester or anhydride (for R^2 = $-CONR^4R^5$) or the sulfonic acid equivalents (for R^2 is $-SO^2NR^4R^5$); with an amine of formula $-NR^4R^5$;

and thereafter, if necessary:

i) converting a compound of Formula (I) into another compound of Formula (I);

ii) removing any protecting groups; and/or

iii) forming a salt thereof.

PCT/GB2006/002471

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/14 C07D401/14 C07D403/14 C07D413/14 C07D405/14
A61K31/44 A61P3/04 A61P3/06

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)
C07D A61K A61P

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

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/015774 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; BOYD, SCOTT; CAULKETT, PETER,) 27 February 2003 (2003-02-27) cited in the application page 24, line 1 - line 18; claim 1	1-16
Y	WO 2004/076420 A1 (BANYU PHARMA CO LTD) 10 September 2004 (2004-09-10) cited in the application claim 1	1-16
P,Y	-& EP 1 600 442 A (BANYU PHARMA CO LTD) 30 November 2005 (2005-11-30) claim 1	1-16

-/--

[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 document but published on or after the international filing date
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2006	31/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 2005/080359 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; JOHNSTONE, CRAIG; MCKERRECHER,) 1 September 2005 (2005-09-01) claim 1	1-16

INTERNATIONAL SEARCH REPORT

International application No.: PCT/GB2006/002471

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14, 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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 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.

[ ] No protest accompanied the payment of additional search fees.

Information on patent family members

PCT/GB2006/002471

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03015774 A	27-02-2003	AT 323487 T	15-05-2006
		AT 334678 T	15-08-2006
		BR 0212008 A	28-09-2004
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		EP 1420784 A1	26-05-2004
		HU 0401213 A2	28-12-2004
		JP 2005525291 T	25-08-2005
		JP 2005320343 A	17-11-2005
		MX PA04001500 A	14-05-2004
		NO 20040686 A	17-02-2004
		NZ 531193 A	29-07-2005
		US 2005080106 A1	14-04-2005
		ZA 200401015 A	06-05-2005
WO 2004076420 A1	10-09-2004	AU 2004215514 A1	10-09-2004
		BR PI0407810 A	01-03-2006
		CA 2516407 A1	10-09-2004
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		US 2006167053 A1	27-07-2006
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		BR PI0407810 A	01-03-2006
		CA 2516407 A1	10-09-2004
		WO 2004076420 A1	10-09-2004
		MA 27660 A1	01-12-2005
		MX PA05009059 A	19-10-2005
		US 2006167053 A1	27-07-2006
WO 2005080359 A	01-09-2005	AR 047678 A1	01-02-2006

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de Propiedad Intelectual
Oficina Internacional

(43) Fecha de Publicación Internacional
18 de enero de 2007 (18.01.2007)

PCT

(10) Número de Publicación Internacional
WO 2007/007041 A1

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C07D 417/14 (2006.01) *C07D 405/14* (2006.01)
C07D 401/14 (2006.01) *A61K 31/44* (2006.01)
C07D 403/14 (2006.01) *A61P 3/06* (2006.01)
C07D 413/14 (2006.01) *A61P 3/04* (2006.01)

(21) No. Solicitud Internacional: PCT/GB2006/002471

(22) Fecha de Presentación Internacional:
3 de julio de 2006 (03.07.2006)

(25) Idioma de Presentación: Inglés

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(30) Datos relativos a la Prioridad:

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0607977.6	22 de abril de 2006 (22.04.2006)	GB

(71) Solicitante *(para AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BF, BG, BJ, BR, BW, BY, BZ, CA, CF, CG, CH, CI, CM, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GA, GB, GD, GE, GH, GM, GN, GQ, GR, GW, HR, HU, ID, IE, IL, IN, IS, IT, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MC, MD, MK, ML, MN, MR, MW, MX, MZ, NA, NE, NG, NI, NL, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SI, SK, SL, SM, SN, SY, SZ, TD, TG, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, ZA, ZM, ZW únicamente)*: **ASTRAZENECA AB** [SE/SE]; S-SE-151 85 Södertälje (SE).

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(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: **MCKERRECHER, Darren** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **PIKE, Kurt, Gordon** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **WARING, Michael, James** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agente: **GLOBAL INTELLECTUAL PROPERTY**; Astrazeneca Ab, S-SE-151 85 Södertälje (SE).

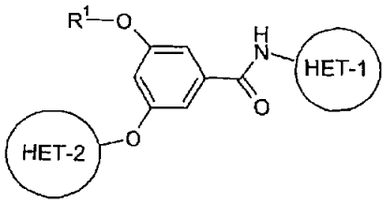
(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, 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, 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: DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES



(I)

(57) Extracto: Compuestos de fórmula (I), en donde R^1, HET-1 y HET-2 son como se describe en la especificación, y sus sales y profármacos, son activadores de glucocinasa (GLK) y, en consecuencia, son útiles en el tratamiento, por ejemplo, de diabetes tipo 2. En igual forma, se describen procesos para preparar compuestos de fórmula (I).

WO 2007/007041 A1

DERIVADOS DE HETEROARILBENZAMIDA PARA USO COMO ACTIVADORES DE GLK EN EL TRATAMIENTO DE DIABETES

La presente invención se refiere a un grupo de compuestos de benzoil amino heterociclilo, que son útiles en el tratamiento o prevención de una enfermedad o afección mediada por glucocinasa (GLK o GK), que lleva a un umbral de glucosa disminuido para secreción de insulina. Adicionalmente se prevé que los compuestos disminuyen la glucosa sanguínea aumentando la absorción de glucosa hepática. Tales compuestos pueden tener utilidad en el tratamiento de diabetes tipo 2 y obesidad. La invención se relaciona asimismo con composiciones farmacéuticas que comprenden tales compuestos y a métodos de tratamiento de enfermedades mediadas por GLK usando dichos compuestos.

En la célula β pancreática y las células hepatoparenquimatosas el principal transportador de glucosa de la membrana plasmática es GLUT2. Bajo concentraciones de glucosa fisiológicas la tasa a la cual GLUT2 transporta glucosa a través de membrana no es limitante respecto a la tasa general de absorción de glucosa en estas células. La tasa de absorción de glucosa está limitada por la tasa de fosforilación de glucosa con respecto a glucosa-6-fosfato (G-6-P) que se cataliza por glucocinasa (GLK) [1]. La GLK tiene una elevada Km (6-10mM) para la glucosa y no se inhibe por concentraciones fisiológicas de G-6-P [1]. La expresión de GLK se limita a unos cuantos tejidos y tipos de células, muy notablemente células β pancreáticas y células hepáticas (hepatocitos) [1]. En estas células la actividad GLK es limitante de la tasa de utilización de glucosa y, en consecuencia, regula la magnitud de secreción de insulina inducida por la glucosa y síntesis de glucógeno hepático. Estos procesos son críticos en el mantenimiento de la homeostasis de glucosa total en el cuerpo y ambos son disfuncionales en la diabetes [2].

En un sub-tipo de diabetes, Diabetes de la Edad Madura de los Jóvenes Tipo 2 (MODY-2), la diabetes es causada por la pérdida de GLK de mutaciones de función [3, 4]. La hiperglicemia en pacientes MODY-2

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resulta de la utilización defectuosa de glucosa en el páncreas y el hígado [5]. La utilización defectuosa de glucosa en el páncreas de pacientes MODY-2 se traduce en un umbral incrementado para la secreción de insulina estimulada por glucosa. Inversamente, mutaciones raras activadoras de GLK reducen este umbral, lo cual se traduce en hiperinsulinismo familiar [6, 6a, 7]. Además de la actividad GLK reducida observada en diabéticos MODY-2, se disminuye asimismo la actividad glucocinasa hepática en diabéticos tipo 2 [8]. De manera importante, la sobreexpresión selectiva hepática o global de GLK previene o revierte el desarrollo del fenotipo diabético en los dos modelos genéticos y dietéticos de la enfermedad [9-12]. Más aún, el tratamiento agudo de diabéticos tipo 2 con fructosa mejora la tolerancia a la glucosa mediante la estimulación de la utilización de glucosa hepática [13]. Se cree que este efecto está mediado por un aumento inducido por fructosa en la actividad GLK citosólica en el hepatocito por el mecanismo descrito a continuación [13].

La actividad GLK hepática se inhibe mediante la asociación con proteína reguladora GLK (GLKRP). El complejo GLK/GLKRP se estabiliza por fructosa-6-fosfato (F6P), que se une a la GLKRP, y se desestabiliza por el desplazamiento de este fosfato de azúcar por fructosa-1-fosfato (F1P). El F1P se genera por fosforilación mediada por fructocinasa de fructosa dietética. En consecuencia, la integridad del complejo GLK/GLKRP y la actividad GLK hepática se regula en una manera dependiente de la nutrición ya que F6P es dominante en el estado pos-absorción, mientras que F1P predomina en el estado pos-prandial. En contraste con el hepatocito, la célula β pancreática expresa GLK en la ausencia de GLKRP. Por lo tanto, la actividad GLK de la célula β se regula extensivamente por la disponibilidad de su sustrato, glucosa. Moléculas pequeñas pueden activar la GLK ya sea directamente o a través de la desestabilización del complejo GLK/GLKRP. Se prevé que la primera clase de compuestos estimula la utilización de glucosa tanto en el hígado como el páncreas, mientras que se anticipa que la última actúa exclusivamente en el hígado. No obstante, se prevé que compuestos con

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uno cualquiera de los dos perfiles son terapéuticamente benéficos en tratar diabetes tipo 2, ya que esta enfermedad se caracteriza por una utilización defectuosa de la glucosa en ambos tejidos.

GLK, GLKRP y el canal K_{ATP} se expresan en neuronas del hipotálamo, una región del cerebro que es importante en la regulación del balance de energía y el control de la ingesta de alimentos [14-18]. Se ha demostrado que estas neuronas expresan neuropéptidos orécticos y anorécticos [15, 19, 20] y se ha asumido que son las neuronas que detectan la glucosa en el hipotálamo, las cuales o bien se inhiben o bien se excitan por cambios en las concentraciones de glucosa ambiente [17, 19, 21, 22]. La capacidad de estas neuronas de detectar cambios en los niveles de glucosa es defectuosa en una variedad de modelos genéticos y experimentalmente inducidos de obesidad [23-28]. La infusión intracerebroventricular (icv) de análogos de glucosa, que son inhibidores competitivos de glucocinasa, estimulan la ingesta de alimentos en ratas flacas [29, 30]. En contraste, la infusión icv de glucosa suprime la ingestión de alimentos [31]. Por consiguiente, activadores de pequeñas moléculas de GLK pueden disminuir la ingesta de alimentos y el aumento de peso a través de los efectos centrales sobre la GLK. Por lo tanto, los activadores de GLK tener uso terapéutico en tratar desórdenes alimenticios, incluida la obesidad, además de la diabetes. Los efectos hipotalámicos serán aditivos o sinérgicos a los efectos de los mismos compuestos que actúan en el hígado y/o el páncreas normalizando la homeostasis de la glucosa, para el tratamiento de diabetes tipo 2. En consecuencia, el sistema GLK/GLKRP puede describirse como un objetivo potencial "Diabesity" (benéfico en Diabetes y Obesidad).

La GLK se expresa igualmente en células entero-endocrinas específicas, donde se cree que controlan la secreción sensible a la glucosa de los péptidos de incretina GIP (polipéptido insulinotrópico dependiente de glucosa) y GLP-1 (Péptido-1 Similar al Glucagón) de células K del intestino y células L respectivamente (32, 33, 34). Por consiguiente, activadores de molécula pequeña de GLK pueden tener efectos benéficos

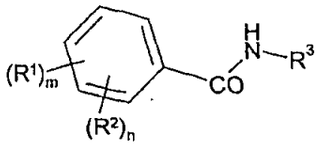
adicionales sobre la secreción insulina, función y supervivencia de la célula β y el peso corporal como consecuencia de estimular la secreción de GIP y GLP-1 de estas dos células entero-endocrinas.

En WO00/58293 y WO01/44216 (Roche), se describe una serie de compuestos de bencilcarbamoilo como activadores de glucocinasa. El mecanismo por el cual tales compuestos activan la GLK se evalúa midiendo el efecto directo de tales compuestos en un análisis en el cual la actividad GLK se asocia con la producción de NADH que, a su vez, se cuantifica ópticamente – ver detalles del análisis *in vitro* descrito más adelante. Los compuestos de la presente invención pueden activar la GLK directamente o pueden activar la GLK inhibiendo la interacción de GLKRP con GLK.

Otros activadores de GLK se han descrito en WO03/095438 (fenilacetamidas sustituidas, Roche), WO03/055482 (derivados de carboxamida y sulfonamida, Novo Nordisk), WO2004/002481 (derivados de arilcarbonilo, Novo Nordisk), y en WO03/080585 (benzoilaminoheterociclos amino-sustituidos, Banyu).

Nuestra Solicitud Internacional Número: WO03/000267 describe un grupo de ácidos benzoil amino piridil carboxílicos, los cuales son activadores de la enzima glucocinasa (GLK).

Nuestra Solicitud Internacional Número: WO03/015774 describe compuestos de la Fórmula (A):



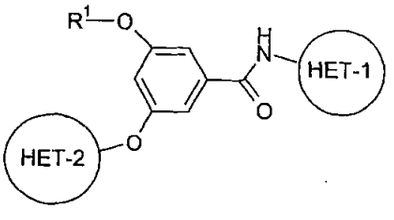
(A)

en donde R^3 es un heterociclo sustituido distinto de un piridilo sustituido con ácido carboxílico.

La Solicitud Internacional WO2004/076420 (Banyu) describe compuestos que son generalmente un subconjunto de los descritos en WO 03/015774, en donde por ejemplo R^1 es éter alquílico (sustituido y R^2 es fenoxi (sustituido).

Sorpresivamente hemos descubierto un pequeño grupo de compuestos, generalmente un subgrupo seleccionado de los descritos en WO 03/015774, los cuales poseen por lo general una potencia superior para la enzima GLK y propiedades físicas más ventajosas, incluidas, por ejemplo, mayor solubilidad acuosa, permeabilidad más alta, y/o unión a proteína plasmática más baja. En consecuencia, se esperaría que tales compuestos con un balance de estas propiedades exhiban niveles más elevados de fármaco libre en el plasma y eficacia superior *in vivo* luego de la medicación oral determinados, por ejemplo, por actividad en Pruebas de Tolerancia a la Glucosa Oral (OGTTs). Por lo tanto, se esperaría que este grupo de compuestos proporcione una exposición oral superior con una dosis más baja y, con ello, sean particularmente idóneos para uso en el tratamiento o prevención de una enfermedad o afección mediada por GLK. Los compuestos de la invención pueden tener además una potencia superior y/o propiedades físicas ventajosas (como se describe anteriormente) y/o perfiles favorables de toxicidad y/o perfiles metabólicos favorables en comparación con otros activadores de GLK conocidos en el arte, así como los descritos en WO 03/015774.

Por consiguiente, de acuerdo con el primer aspecto de la invención se provee un compuesto de Fórmula (I):



(I)

en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2- hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-

hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo enlazado a C, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y de manera opcional 1 ó 2 heteroátomos de anillo adicionales, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^7 y/o en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^6;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, que contiene 1, 2 ó 3 heteroátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^{10};

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de metilo, trifluorometilo y halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)- y en donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 ó 2 sustituyentes seleccionados independientemente de R^8 y/o en un átomo de nitrógeno disponible por un sustituyente seleccionado de R^9; o R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, bicíclico, de 6-10 miembros, que contiene opcionalmente 1 átomo de nitrógeno adicional (aparte del átomo N enlazante), en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)-; anillo

que se sustituye opcionalmente en un átomo de carbono disponible por 1 sustituyente seleccionado de hidroxi y R^3 o en un átomo de nitrógeno disponible por metilo;

R^6 se selecciona independientemente de (1-4C)alquilo, halo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo;

R^7 se selecciona independientemente de (1-4C)alquilo, halo(1-4C)alquilo, dihalo(1-4C)alquilo, trihalo(1-4C)alquilo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo;

R^8 se selecciona de hidroxi, (1-4C)alcoxi, (1-4C)alquilo, aminocarbonilo, (1-4C)alquilaminocarbonilo, di(1-4C)alquilaminocarbonilo, (1-4C)alquilamino, di(1-4C)alquilamino, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -S(O)p(1-4C)alquilo;

R^9 se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, aminocarbonilo, (1-4C)alquilaminocarbonilo, di(1-4C)alquilaminocarbonilo, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -S(O)p(1-4C)alquilo;

R^{10} se selecciona de (1-4C)alquilo, (3-6C)cicloalquilo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, -C(O)(1-4C)alquilo, bencilo, y (1-4C)alquilsulfonilo;

p es (independientemente de cada ocurrencia) 0, 1 ó 2;

o su sal.

En otro aspecto de la invención se provee un compuesto de fórmula (I) como se define anteriormente en donde R^1 se selecciona de isopropilo, but-2-ilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 1-fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo;

o su sal.

En otro aspecto de la invención se provee un compuesto de fórmula (I) como se define anteriormente en donde R^1 se selecciona de isopropilo, but-2-ilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo; o su sal.

En otro aspecto de la invención se provee un compuesto de fórmula (I) como se define anteriormente en donde R^3 es halo; o su sal.

En otro aspecto de la invención se provee un compuesto de fórmula (I) como se define anteriormente en donde R^7 se selecciona independientemente de (1-4C)alquilo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo; o su sal.

Se observará que, donde las definiciones de grupos heterocililo HET-1 y HET-2 abarcan anillos heteroarilo, que pueden sustituirse en nitrógeno, tal sustitución puede no resultar en átomos de nitrógeno cuaternario cargados, retiro de la aromaticidad del anillo o estructuras inestables. Se observará que las definiciones de HET-1 y HET-2 no pretenden incluir cualquiera de los enlaces O-O, O-S o S-S. Se observará que las definiciones de HET-1 y HET-2 no pretenden incluir estructuras inestables.

Se entenderá que cualquier átomo de carbono en HET-1 puede sustituirse únicamente por un grupo R^6 con el fin de mantener la aromaticidad del anillo. Hasta dos átomos de carbono diferentes en un anillo HET-1 pueden sustituirse por un grupo R^6, cada uno de los cuales puede ser el mismo o diferente, siempre que la estructura así formada sea estable y aromática.

Se entenderá que cualquier átomo de carbono individual en HET-2 puede sustituirse únicamente por un grupo R^3 con el fin de mantener la aromaticidad del anillo. Hasta dos átomos de carbono diferentes en el anillo HET-2 pueden sustituirse por un grupo R^3, cada uno de los cuales

puede ser el mismo o diferente, siempre que la estructura así formada sea estable y aromática.

Se entenderá que R^8 puede estar presente en cualquiera o todos los átomos de carbono disponibles en el anillo heterocíclico formado por NR^4R^5; cada átomo de carbono puede sustituirse con 1 ó 2 grupos R^8, los cuales pueden ser los mismos o diferentes, siempre que la estructura así formada sea estable (por lo tanto, por ejemplo, no se pretende cubrir la sustitución gem-dihidroxi).

Se entenderá que donde un compuesto de la fórmula (I) contiene más de un grupo R^5, éstos pueden ser los mismos o diferentes.

Se entenderá que donde un compuesto de la fórmula (I) contiene más de un grupo R^3, éstos pueden ser los mismos o diferentes.

Una convención similar se aplica para todos los demás grupos y sustituyentes en un compuesto de Fórmula (I), como se define más arriba en el texto.

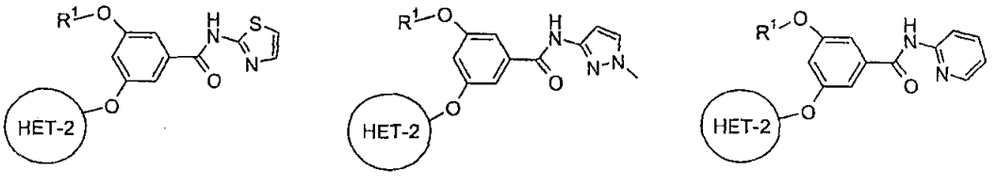
Compuestos de Fórmula (I) pueden formar sales que están dentro del ámbito de la invención. Se prefieren sales farmacéuticamente aceptables, aunque otras sales pueden ser útiles, por ejemplo, en aislar o purificar compuestos.

En otro aspecto, la invención se refiere a Compuestos de Fórmula (I), como se define más arriba en el texto o a una sal farmacéuticamente aceptable.

En esta especificación el término genérico "alquilo" incluye grupos de cadena recta y cadena ramificada. No obstante, referencias a grupos alquilo individuales tales como "propilo" son específicos de la versión de cadena recta únicamente y las referencias a grupos alquilo de cadena ramificada individuales tales como *t*-butilo son específicos de la versión de cadena ramificada únicamente. Por ejemplo, "(1-4C)alquilo" incluye metilo, etilo, propilo, isopropilo y *t*-butilo. Una convención análoga se aplica a otros términos genéricos.

Para evitar dudas, la referencia al grupo HET-1 que contiene un nitrógeno en la posición 2, tiene como finalidad referirse a la posición 2

relativa al átomo de nitrógeno de amida a la cual se une el grupo. Por ejemplo, HET-1 incluye, pero no se limita a las siguientes estructuras:



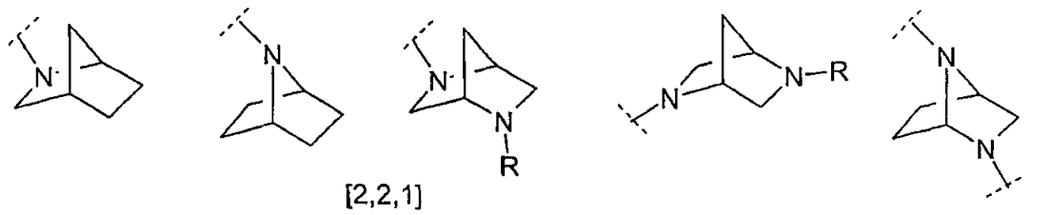
Ejemplos apropiados de HET-1 como anillo heteroarilo enlazado a C, de 5 ó 6 miembros, como se define más arriba en el texto, incluyen tiazolilo, isotiazolilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo, oxazolilo, isoxazolilo, oxadiazolilo y triazolilo.

Ejemplos apropiados de HET-2 incluyen tienilo, furilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo, oxazolilo, isoxazolilo, oxadiazolilo y triazolilo. Otros ejemplos apropiados de HET-2 incluyen heterociclos aromáticos donde un átomo de nitrógeno o azufre de anillo se ha oxididado, pero se ha preservado la aromaticidad, por ejemplo un N-óxido de piridina. Otros ejemplos apropiados de HET-2 incluyen tiazolilo, piridilo, pirazinilo, piridazinilo y pirimidinilo.

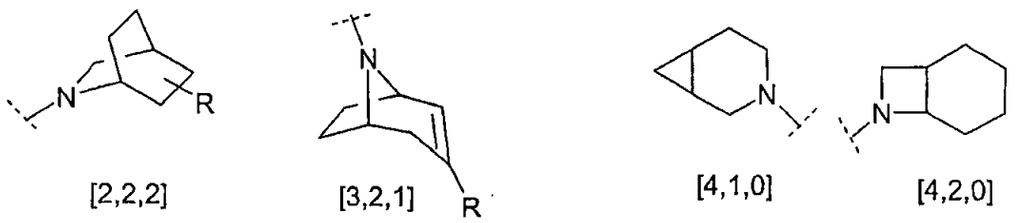
Ejemplos apropiados para un anillo de 4-7 miembros formado por R^4 y R^5, junto con el nitrógeno al cual se unen, como se define anteriormente, incluyen morfolino, piperidinilo, piperazinilo, pirrolidinilo, azetidinilo, homopiperazinilo, homo-morfolino, homo-tiomorfolino (y sus versiones en donde el azufre se oxida en un grupo SO o $S(O)_2$) y homo-piperidinilo. Otro ejemplo apropiado es tiomorfolino (y sus versiones en donde el azufre se oxida en un grupo SO o $S(O)_2$).

Ejemplos apropiados para un anillo heterocíclico bicíclico de 6-10 miembros formado por R^4 y R^5, junto con el nitrógeno al cual se unen, como se define anteriormente, son un anillo heterociclilo, saturado o parcialmente insaturado, bicíclico, tales como los ilustrados por las estructuras mostradas más adelante (en donde la línea punteada indica el

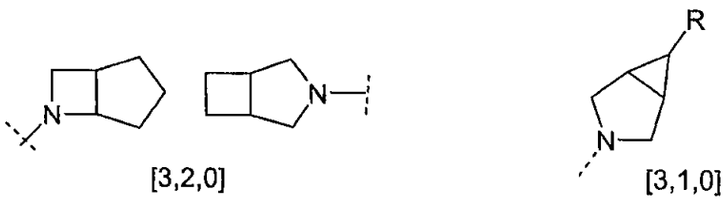
punto de unión al resto de la molécula y en donde R representa los sustituyentes opcionales para carbono o nitrógeno definidos anteriormente):



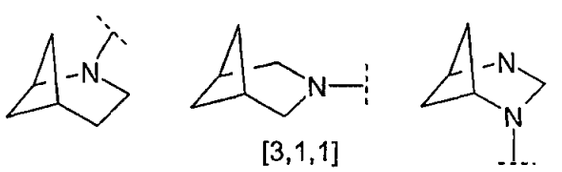
[2,2,1]



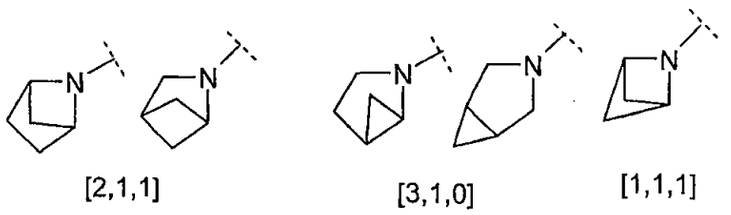
[2,2,2] [3,2,1] [4,1,0] [4,2,0]



[3,2,0] [3,1,0]



[3,1,1]



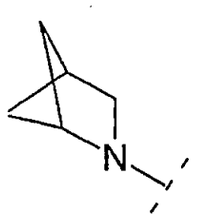
[2,1,1] [3,1,0] [1,1,1]

En particular tal sistema de anillo es un sistema [2,2,1] tal como



(7-azabiciclo[2.2.1]hept-7-ilo).

En otra incorporación, tal sistema de anillo es un sistema [2,2,1] tal como



(2-azabiciclo[2.1.1]hex-2-ilo).

Ejemplos de **(1-4C)alquilo** incluyen metilo, etilo, propilo, isopropilo, butilo y *terc*-butilo; ejemplos de **(3-6C)cicloalquilo** incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo; ejemplos de **halo** incluyen fluoro, cloro, bromo y yodo; ejemplos de halo(1-4C)alquilo incluyen fluorometilo, clorometilo, fluoroetilo, cloroetilo, fluoropropilo y fluorobutilo; ejemplos de **dihalo(1-4C)alquilo** incluyen difluorometilo, 1,1-difluoroet-2-ilo, 1,2-difluoroet-2-ilo, 1,1-dicloroet-2-ilo, 1,2-dicloroet-2-ilo, y 1,1-difluoroprop-3-ilo; ejemplos de **trihalo(1-4C)alquilo** incluyen trifluorometilo y 1,1,1-trifluoroet-2-ilo; ejemplos de **hidroxi(1-4C)alquilo** incluyen hidroximetilo, 1-hidroxietilo, 2-hidroxietilo, 2-hidroxipropilo, 3-hidroxipropilo, 1-hidroxiisopropilo y 4-hidroxibutilo; ejemplos de **(1-4C)alcoxi(1-4C)alquilo** incluyen metoximetilo, etoximetilo, *terc*-butoximetilo, 2-metoxietilo, 2-etoxietilo, metoxipropilo, 2-metoxipropilo y metoxibutilo; ejemplos de **(1-4C)alcoxi** incluyen metoxi, etoxi, propoxi, isopropoxi, butoxi y *terc*-butoxi; ejemplos de **(1-4C)alquilS(O)p(1-4C)alquilo (donde p es 0, 1 ó 2)** incluyen metilsulfinilmetilo, etilsulfinilmetilo, etilsulfiniletilo, metilsulfinilpropilo, metilsulfinilbutilo, metilsulfonilmetilo, etilsulfonilmetilo, etilsulfoniletilo, metilsulfonilpropilo, metilsulfonilbutilo, metiltiometilo, etiltiometilo, etiltioetilo, metiltiopropilo, y metiltiobutilo; ejemplos de **(1-4C)alquilsulfonilo** incluyen metilsulfonilo, etilsulfonilo, propilsulfonilo, isopropilsulfonilo y *terc*-butilsulfonilo; ejemplos de **-S(O)p(1-4C)alquilo** incluyen (1-4C)alquilsulfonilo, metilsulfinilo, etilsulfinilo, propilsulfinilo, isopropilsulfinilo, *terc*-butilsulfinilo, metiltio, etiltio, propiltio, isopropiltio y *terc*-butiltio; ejemplos de **amino(1-4C)alquilo** incluyen aminometilo, aminoetilo, 2-aminopropilo, 3-aminopropilo, 1-aminoisopropilo y 4-aminobutilo; ejemplos de **(1-4C)alquilamino(1-4C)alquilo** incluyen (N-metil)aminometilo, (N-etil)aminometilo, 1-((N-metil)amino)etilo, 2-((N-metil)amino)etilo, (N-etil)aminoetilo, (N-metil)aminopropilo, y 4-((N-metil)amino)butilo; ejemplos de **di(1-4C)alquilamino(1-4C)alquilo** incluyen dimetilaminometilo, metil(etil) aminometilo, metil(etil)aminoetilo, (N,N-dietil)aminoetilo, (N,N-dimetil)aminopropilo y (N,N-dimetil)aminobutilo;

ejemplos de **-C(O)(1-4C)alquilo** y **(1-4C)alquilcarbonilo** incluyen metilcarbonilo, etilcarbonilo, propilcarbonilo y *terc*-butil carbonilo; ejemplos de **(1-4C)alquilamino** incluyen metilamino, etilamino, propilamino, isopropilamino, butilamino y *terc*-butilamino; ejemplos de **di(1-4C)alquilamino** incluyen dimetilamino, dietilamino, N-metil-N-etilamino, dipropilamino, N-isopropil-N-metilamino y dibutilamino; ejemplos de **(1-4C)alquilaminocarbonilo** incluyen metilaminocarbonilo, etilaminocarbonilo, propilaminocarbonilo, isopropilaminocarbonilo, butilaminocarbonilo y *terc*-butilaminocarbonilo; ejemplos de **di(1-4C)alquilaminocarbonilo** incluyen dimetilaminocarbonilo, dietilaminocarbonilo, N-metil-N-etilaminocarbonilo, dipropilaminocarbonilo, N-isopropil-N-metilaminocarbonilo y dibutilaminocarbonilo.

Hay que entender que, en la medida en que algunos de los Compuestos de Fórmula (I) ya definidos, puedan existir en formas racémicas u ópticamente activas en virtud de uno o más átomos de carbono asimétricos, la invención incluye en su definición cualquier forma racémica u ópticamente activa que posea la propiedad de estimular GLK directamente o inhibiendo la interacción GLK/GLKRP. La síntesis de formas ópticamente activas puede llevarse a cabo por técnicas estándar de química orgánica bien conocidas en el arte, por ejemplo por síntesis de materiales de partida ópticamente activos o por resolución de una forma racémica. Hay que entender asimismo que ciertos compuestos pueden existir en formas tautoméricas y que la invención se refiere igualmente a cualquiera y a todas las formas tautoméricas de los compuestos de la invención que activan la GLK.

Se entiende igualmente que ciertos compuestos de la fórmula (1) y sus sales pueden existir en formas solvatadas y no solvatadas tales como, por ejemplo, formas hidratadas. Hay que entender que la invención abarca la totalidad de tales formas solvatadas que activan GLK.

En otro aspecto, la invención se refiere a compuestos de fórmula (I) como se define anteriormente o a su profármaco. Ejemplos apropiados de

profármacos de compuestos de fórmula (I) son ésteres hidrolizables *in vivo* de los compuestos de fórmula (I). En consecuencia, en otro aspecto, la invención se refiere a compuestos de fórmula (I), como se define anteriormente, o a su éster hidrolizable *in vivo*.

En una incorporación de la invención se proveen Compuestos de Fórmula (I), en una incorporación alternativa se proveen sales farmacéuticamente aceptables de Compuestos de Fórmula (I), en una incorporación alternativa más se proveen ésteres hidrolizables *in vivo* de Compuestos de Fórmula (I), y en una incorporación alternativa más se proveen sales farmacéuticamente aceptables de ésteres hidrolizables *in vivo* de Compuestos de Fórmula (I).

Los compuestos de la invención pueden administrarse en la forma de un profármaco. Un profármaco es un bioprecursor o compuesto farmacéuticamente aceptable que es degradable en el cuerpo para producir un compuesto de la invención (tal como un éster o amida de un compuesto de la invención, particularmente un éster hidrolizable *in vivo*). Varias formas de profármacos se conocen en el arte. Para ejemplos de tales derivados de profármacos, véase:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press,1985);

b) A Textbook of Drug Design y Development, edited by Krogsgaard-Larsen;

c) H. Bundgaard, Chapter 5 "Design y Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); y

f) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

El contenido de los documentos anteriormente citados se incorpora aquí por referencia.

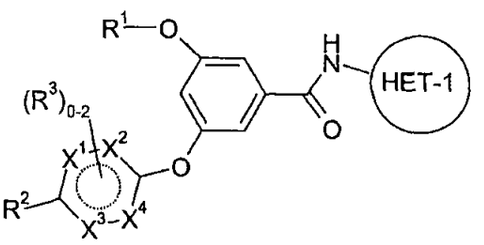
Ejemplos de profármacos son los siguientes. Un éster hidrolizable *in vivo* de un compuesto de la invención, que contiene un grupo carboxi o hidroxi es, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el cuerpo humano o animal para producir el ácido precursor o alcohol. Ésteres farmacéuticamente aceptables para carboxi incluyen ésteres de C_1 a C_6 alcoximetilo por ejemplo metoximetilo, ésteres de C_1 a C_6 alcanoiloximetilo por ejemplo pivaloiloximetilo, ésteres de ftalidilo, C_3 a C_8 cicloalcoxicarboniloxi, ésteres de C_1 a C_6alquilo por ejemplo 1-ciclohexilcarboniloxietilo; ésteres de 1,3-dioxolen-2-onilmetilo, por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres de C_{1-6}alcoxicarboniloxietilo.

Un éster hidrolizable *in vivo* de un compuesto de la invención que contiene un grupo hidroxi incluye ésteres inorgánicos tales como ésteres de fosfato (incluidos ésteres cíclicos fosforamídicos) y éteres de α-aciloxialquilo y compuestos relacionados que, como resultado de la hidrólisis *in vivo* del éster, se descomponen para producir el grupo(s) hidroxi precursor. Ejemplos de éteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Un selección de grupos formadores de ésteres hidrolizables *in vivo* para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxicarbonilo (para producir ésteres de alquilcarbonato), dialquilcarbamoilo y N-(dialquilaminoetil)-N-alquilcarbamoilo (para producir carbamatos), dialquilaminoacetilo y carboxiacetilo.

Una sal farmacéuticamente aceptable, apropiada, de compuesto de la invención es, por ejemplo, una sal de adición de ácido de un compuesto de la invención que es suficientemente básico, por ejemplo, una sal de adición de ácido con, por ejemplo, un ácido orgánico o inorgánico, ácido por ejemplo clorhídrico, bromhídrico, sulfúrico, fosfórico, trifluoroacético, cítrico o maleico. Adicionalmente, una sal farmacéuticamente aceptable, apropiada, de un derivado de benzoxazinona de la invención, que es suficientemente ácido, es una sal de metal alcalino, por ejemplo una sal de sodio o potasio, una sal de metal alcalinotérreo, por ejemplo una sal de

magnesio o calcio, una sal de amonio o una sal con una base orgánica que proporciona un catión fisiológicamente aceptable, por ejemplo una sal con metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris-(2-hidroxietil)amina.

En un aspecto adicional de la invención, se provee un compuesto de fórmula (I), el cual es un compuesto de fórmula (IA), o su sal:



(IA)

en donde cada uno de X^1, X^2 y X^3 se selecciona independientemente de CH, N, S y O;

X^4 está ausente (para conformar un anillo de 5 miembros) o se selecciona de CH, N, O y S;

siempre que por lo menos uno de X^1, X^2, X^3 y X^4 sea CH, y siempre que no haya enlaces O-O, O-S o S-S en el anillo;

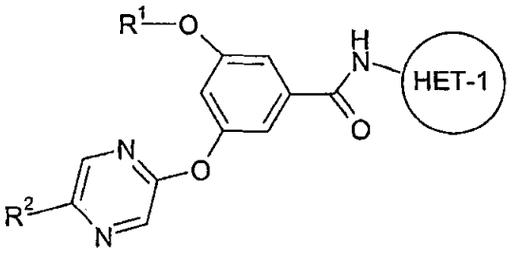
R^3, si se halla presente, se selecciona de metilo, trifluorometilo y halo;

R^1, R^2 y HET-1 son como se definen para un compuesto de fórmula (I).

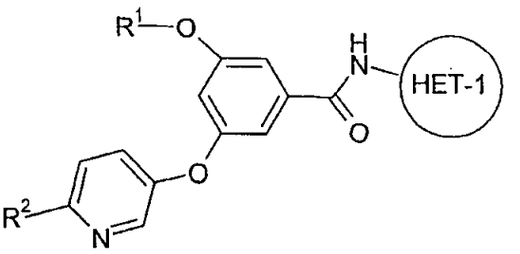
Se entenderá que el círculo punteado dentro del anillo que contiene X^1 a X^4 (es decir, el anillo HET-2) tiene como fin indicar que el anillo es aromático, si bien el número exacto y la posición de los enlaces dobles dependerán de la naturaleza de X^1 a X^4.

Debe entenderse por lo general que las referencias en esta solicitud a un compuesto de fórmula (I) se aplican por igual a un compuesto de fórmula (IA), se declare específicamente o no, a menos que el contexto indique lo contrario.

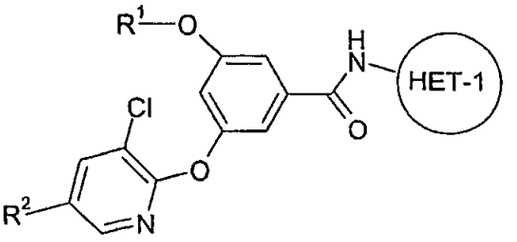
Ejemplos particulares de compuestos de fórmula (I) y (IA) incluyen compuestos de fórmulas (IB), (IC) y/o (ID):



(IB)



(IC)

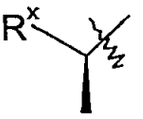


(ID)

en donde R^1, R^2 y HET-1 son como se definen para un compuesto de fórmula (I).

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 definidas más arriba o más adelante en el texto. En particular, cada uno puede emplearse como una limitación individual a la definición más amplia de fórmula (I) o (IA). Además, cada uno de los siguientes valores puede utilizarse en combinación con uno o más de los demás valores siguientes para limitar la definición más amplia de fórmula (I) o (IA) o para limitar cualesquiera definiciones más restringidas de fórmula (I) o (IA) en cualquiera de los aspectos indicados más arriba o más adelante. Donde se considere apropiado, cada uno de los siguientes valores puede usarse igualmente para limitar cualquier definición incluida en las fórmulas (IB), (IC) y/o (ID).

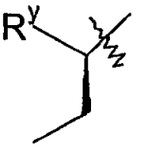
(1) R^1 es de la sub-fórmula X:



(X)

en donde R^x se selecciona de metilo, etilo, trifluorometilo, etinilo, hidroximetilo, hidroxietilo, metoximetilo, fluorometoximetilo, difluorometoximetilo y trifluorometoximetilo; preferiblemente R^x se selecciona de metilo, etilo, trifluorometilo, etinilo, hidroximetilo, hidroxietilo, metoximetilo, fluorometoximetilo y difluorometoximetilo;

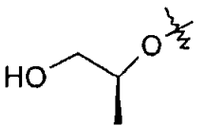
(2) R^1 es de la sub-fórmula Y:



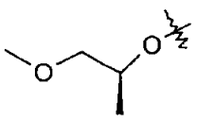
(Y)

en donde R^y se selecciona de hidroximetilo y metoximetilo;

(3) R^1 es 1-hidroxiprop-2-ilo y la configuración es preferiblemente (S), es decir, R^1-O- es:



(4) R^1 es 1-metoxiprop-2-ilo y la configuración es preferiblemente (S), es decir, R^1-O- es:

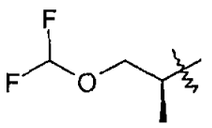


(5) R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, hidroxibut-3-ilo y 1-metoxiprop-2-ilo

(6) R^1 es 1,1,1-trifluoroprop-2-ilo, 1-fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo o 1-trifluorometoxiprop-2-ilo

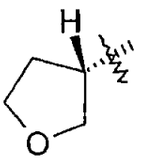
(7) R^1 es 1-fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo o 1-trifluorometoxiprop-2-ilo, particularmente 1-fluorometoxiprop-2-ilo o 1,1-difluorometoxiprop-2-ilo

(8) R^1 es 1,1-difluorometoxiprop-2-ilo, particularmente con la estereoquímica:

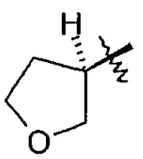


(9) R^1 es tetrahidrofurilo o tetrahidropiranilo

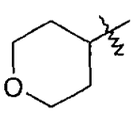
(10) R^1 es tetrahidrofurilo en la configuración (S), es decir:



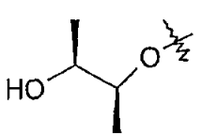
(11) R^1 es tetrahidrofurilo en la configuración (R), es decir:



(12) R^1 es 4-tetrahidropiranilo:



(13) R^1 es 2-hidroxi-but-3-ilo y la configuración es preferiblemente tal que R^1-O- es:



(14) R^1 es 1-hidroxibut-2-ilo o 1-metoxibut-2-ilo

(15) R^1 se selecciona de isopropilo, but-2-ilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo

(16) R^1 se selecciona de 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo y 2-metoxibut-1-ilo

(17) R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1,1-difluorometoxiprop-2-ilo, tetrahidrofurilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo

(18) R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1,1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo

(19) R^1 se selecciona de tetrahidrofurilo, 1-difluorometoxiprop-2-ilo, 1,3-difluoroprop-2-ilo, y 2-hidroxibut-3-ilo

(20) R^1 se selecciona de isopropilo, tetrahidrofurilo, 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo

(21) R^1 se selecciona de 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo, por ejemplo (2*S*)-1-hidroxiprop-2-ilo y (2*S*)-1-metoxiprop-2-ilo

(22) R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2- hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo

(23) R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2- hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo y 1,1-difluorometoxiprop-2-ilo

(24) HET-1 es un anillo heteroarilo de 5 miembros

(25) HET-1 es un anillo heteroarilo de 6 miembros

(26) HET-1 se sustituye con 1 ó 2 sustituyentes seleccionados independientemente de R^6

(27) HET-1 se sustituye con 1 sustituyente seleccionado de R^6

(28) HET-1 se sustituye con 1 sustituyente seleccionado de R^7

(29) HET-1 no se sustituye

(30) HET-1 se selecciona de tiazolilo, isotiazolilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo, oxazolilo, isoxazolilo, oxadiazolilo, y triazolilo

(31) HET-1 se selecciona de tiazolilo, isotiazolilo, tiadiazolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo y oxadiazolilo

(32) HET-1 se selecciona de piridilo, pirazinilo, piridazinilo y pirimidinilo

(33) HET-1 se selecciona de tiazolilo, pirazolilo y oxazolilo

(34) HET-1 se selecciona de tiadiazolilo y oxadiazolilo

(35) HET-1 se selecciona de 1,3,4-tiadiazolilo y 1,3,4-oxadiazolilo

(36) HET-1 se selecciona de 1,2,4-oxadiazolilo y 1,2,4-oxadiazolilo

(37) HET-1 es pirazolilo, particularmente N-metilpirazolilo

(38) HET-1 es pirazinilo

(39) HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo

(40) HET-1 se selecciona de tiazolilo, pirazolilo, y tiadiazolilo, sustituido opcionalmente con (1-4C)alquilo

(41) HET-1 es pirazolilo, particularmente N-metilpirazolilo

(42) HET-1 es pirazolilo (sustituido opcionalmente con etilo, isopropilo o 1 ó 2 metilo), tiazolilo (sustituido opcionalmente con metilo), pirazinilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro), isoxazolil (sustituido opcionalmente con metilo) y tiadiazolilo (sustituido opcionalmente con metilo)

(43) HET-1 es pirazolil (sustituido opcionalmente con etilo, isopropilo, difluorometilo, o 1 ó 2 metilo), tiazolilo (sustituido opcionalmente con metilo), pirazinilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro), isoxazolilo (sustituido opcionalmente con metilo) y tiadiazolilo (sustituido opcionalmente con metilo)

(44) HET-1 se selecciona de pirazinilo (sustituido opcionalmente con metilo), pirazolilo ((sustituido opcionalmente en carbono por metilo), metiltiadiazolilo (particularmente 1,2,4-tiadiazol-5-ilo, más particularmente 3-metil-1,2,4-tiadiazol-5-ilo), tiazolilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro) e isoxazolilo

(45) HET-1 es N-difluorometilpirazolilo

(46) HET-1 es 5-metilpirazin-2-ilo

(47) HET-1 es pirazolilo (sustituido opcionalmente con etilo, isopropilo, difluorometilo, o 1 ó 2 metilo), tiazolilo (sustituido opcionalmente con

metilo), pirazinilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro), isoxazolilo (sustituido opcionalmente con metilo) y tiadiazolilo (sustituido opcionalmente con metilo); y R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1,1-difluorometoxiprop-2-ilo, tetrahidrorurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo; cuando HET-1 es pirazolilo no sustituido en nitrógeno (es decir, NH-pirazolilo), particularmente R^1 se selecciona de 1-metoxiprop-2-ilo, isopropilo, y tetrahidrofurilo

(48) HET-1 es pirazolilo (sustituido opcionalmente en carbono con metilo), tiazolilo (sustituido opcionalmente con metilo), pirazinilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro), isoxazolilo y metiltiadiazolilo (particularmente 3-metil-1,2,4-tiadiazol-5-ilo); R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1,1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo; cuando HET-1 es pirazolilo, particularmente R^1 se selecciona de 1-metoxiprop-2-ilo, isopropilo, y tetrahidrofurilo

(49) HET-1 es metilpirazinilo y R^1 se selecciona de 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo, por ejemplo (2*S*)-1-hidroxiprop-2-ilo y (2*S*)-1-metoxiprop-2-ilo

(50) HET-1 es pirazolilo y R^1 se selecciona de isopropilo, tetrahidrofurilo y 1-metoxiprop-2-ilo, por ejemplo (2*S*)-1-metoxiprop-2-ilo

(51) R^6 se selecciona de (1-4C)alquilo, halo, hidroxi(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo

(52) R^6 se selecciona de metilo, etilo, bromo, cloro, fluoro, hidroximetilo, metoximetilo, aminometilo, N-metilaminometilo, dimetilaminometilo

(53) R^6 se selecciona de (1-4C)alquilo, halo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo, y di(1-4C)alquilamino(1-4C)alquilo

(54) R^6 se selecciona de metilo, etilo, bromo, cloro, fluoro, hidroximetilo y metoximetilo

(55) R^6 se selecciona de metilo, etilo, cloro y fluoro

(56) R^6 es metilo o fluoro, preferiblemente metilo

(57) R^6 se selecciona de metilo, etilo, bromo, cloro, fluoro, aminometilo, N-metilaminometilo, dimetilaminometilo, hidroximetilo y metoximetilo

(58) R^6 se selecciona de metilo, etilo, aminometilo, N-metilaminometilo, dimetilaminometilo, hidroximetilo y metoximetilo

(59) R^6 se selecciona de metilo, etilo, isopropilo y metoximetilo

(60) cuando 2 sustituyentes R^6 están presentes, ambos se seleccionan de metilo, etilo, bromo, cloro y fluoro; preferiblemente ambos son metilo

(61) R^6 se selecciona de (1-4C)alquilS(O)p(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo

(62) R^7 se selecciona de (1-4C)alquilo, hidroxi(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo

(63) R^7 se selecciona de metilo, etilo, hidroximetilo, metoximetilo, aminometilo, N-metilaminometilo, dimetilaminometilo

(64) R^7 se selecciona de (1-4C)alquilo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo, y di(1-4C)alquilamino(1-4C)alquilo

(65) R^7 se selecciona de metilo, etilo, aminometilo, N-metilaminometilo, y dimetilaminometilo

(66) R^7 se selecciona de metilo, etilo, hidroximetilo y metoximetilo

(67) R^7 se selecciona de metilo, isopropilo y etilo

(68) R^7 se selecciona de metilo, isopropilo, difluorometilo y etilo

(69) R^7 se selecciona de isopropilo y difluorometilo, particularmente difluorometilo

(70) R^7 se selecciona de metilo y etilo

(71) R^7 es metilo

(72) R^7 se selecciona de metilo, etilo, aminometilo, N-metilaminometilo, dimetilaminometilo, hidroximetilo y metoximetilo

(73) R^7 se selecciona de metilo, etilo, isopropilo y metoximetilo

(74) cuando R^7 se selecciona de halo(1-4C)alquilo, dihalo(1-4C)alquilo y trihalo(1-4C)alquilo, cada halo se selecciona de cloro y fluoro, y es en particular fluoro

(75) cuando R^7 se selecciona de halo(1-4C)alquilo, dihalo(1-4C)alquilo y trihalo(1-4C)alquilo, R^7 se selecciona particularmente de fluorometilo, difluoroetilo, difluorometilo y trifluorometilo

(76) HET-2 es un anillo de 5 miembros

(77) HET-2 es un anillo de 6 miembros

(78) HET-2 se selecciona de tienilo, furilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo, oxazolilo, isoxazolilo y oxadiazolilo

(79) HET-2 se selecciona de tienilo, furilo, tiadiazolilo, piridilo, pirazinilo, piridazinilo, pirazolilo, imidazolilo, pirimidinilo y oxadiazolilo

(80) HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y tienilo

(81) HET-2 se selecciona de piridilo, pirazinilo y tiazolilo

(82) HET-2 se selecciona de piridilo, pirazinilo, piridazinilo y tiazolilo

(83) HET-2 se selecciona de piridilo y pirazinilo

(84) HET-2 es pirazinilo

(85) HET-2 se sustituye con a sustituyente seleccionado de R^3

(86) HET-2 tiene un sustituyente nitrógeno seleccionado de R^{10}

(87) R^3 es cloro o fluoro

(88) R^3 es cloro

(89) R^3 es fluoro

(90) R^3 es cloro o metilo

(91) R^3 es fluoro, cloro o metilo

(92) R^2 es $-C(O)NR^4R^5$

(93) R^2 es $-SO_2NR^4R^5$

(94) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo de 4 miembros

(95) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo de 5 miembros

(96) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo de 6 miembros

(97) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo de 7 miembros

(98) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo completamente saturado

(99) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo seleccionado de morfolino, piperidinilo, piperazinilo, pirrolidinilo y azetidinilo

(100) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo seleccionado de pirrolidinilo, morfolino y azetidinilo

(101) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo seleccionado de 7-azabiciclo[2.2.1]hept-7-ilo, pirrolidinilo, morfolino y azetidinilo

(102) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo azetidinilo

(103) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo azetidinilo o pirrolidinilo

(104) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo no sustituido

(105) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo mono-sustituido con un sustituyente R^8 o con un sustituyente R^9

(106) R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo saturado o parcialmente insaturado, bicíclico, de 6-10 miembros

(107) R^8 se selecciona de hidroxi, (1-4C)alcoxi, (1-4C)alquilo

(108) R^8 se selecciona de hidroxi, metoxi y metilo

(109) R^9 se selecciona de (1-4C)alquilo y -C(O)(1-4C)alquilo

(110) R^2 es azetidinilcarbonilo o pirrolidinilcarbonilo, preferiblemente azetidinilcarbonilo (109) R^{10} es (1-4C)alquilo

(111) R^{10} es (3-6C)cicloalquilo

(112) R^{10} es hidroxi(1-4C)alquilo o (1-4C)alcoxi(1-4C)alquilo

(113) R^{10} es -C(O)(1-4C)alquilo

(114) R^{10} es bencilo

(115) R^{10} es (1-4C)alquilsulfonilo

(116) R^{10} es (1-4C)alquilo o bencilo.

De acuerdo con una característica adicional de la invención, se proveen los siguientes grupos preferidos de compuestos de la invención:

En un aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo C-enlazado, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos adicionales de anillo, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un grupo metilo o etilo y/o en 1 ó 2 átomos de carbono disponibles por un grupo metilo o etilo;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, que contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^{10};

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)- y en

donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 ó 2 sustituyentes seleccionados independientemente de R^8 y/o en un átomo de nitrógeno disponible por un sustituyente seleccionado de R^9;

R^8 se selecciona de hidroxi, (1-4C)alcoxi y (1-4C)alquilo;

R^9 se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, y -S(O)p(1-4C)alquilo;

R^{10} se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, bencilo, y (1-4C)alquilsulfonilo;

p es (independientemente de cada ocurrencia) 0, 1 ó 2.

En un aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo C-enlazado, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos adicionales de anillo, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un grupo metilo o etilo y/o en 1 ó 2 átomos de carbono disponibles por un grupo metilo o etilo;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, que contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^{10};

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)- y en donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 ó 2 sustituyentes seleccionados independientemente de R^8 y/o en un átomo de nitrógeno disponible por un sustituyente seleccionado de R^9;

R^8 se selecciona de hidroxi, (1-4C)alcoxi y (1-4C)alquilo;

R^9 se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, y -S(O)p(1-4C)alquilo;

R^{10} se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, bencilo, y (1-4C)alquilsulfonilo; p es (independientemente de cada ocurrencia) 0, 1 ó 2.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2- hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo y 1,1- difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo C-enlazado, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos adicionales de anillo, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un grupo metilo, etilo o isopropilo y/o en 1 ó 2 átomos de carbono disponibles por un grupo metilo, etilo o fluoro;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, que contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un

sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)- y en donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 ó 2 sustituyentes seleccionados independientemente de R^8 y/o en un átomo de nitrógeno disponible por un sustituyente seleccionado de R^9;

R^8 se selecciona de hidroxi, (1-4C)alcoxi y (1-4C)alquilo;

R^9 se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, y -S(O)p(1-4C)alquilo;

R^{10} se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, bencilo, y (1-4C)alquilsulfonilo;

p es (independientemente de cada ocurrencia) 0, 1 ó 2.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo C-enlazado, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos adicionales de anillo, seleccionados independientemente de O, N y S; anillo

que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un grupo metilo, etilo o isopropilo y/o en 1 ó 2 átomos de carbono disponibles por un grupo metilo, etilo o fluoro;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, que contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^{10};

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de metilo y halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)- y en donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 ó 2 sustituyentes seleccionados independientemente de R^8 y/o en un átomo de nitrógeno disponible por un sustituyente seleccionado de R^9;

R^8 se selecciona de hidroxi, (1-4C)alcoxi y (1-4C)alquilo;

R^9 se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, y -S(O)p(1-4C)alquilo;

R^{10} se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, bencilo, y (1-4C)alquilsulfonilo;

p es (independientemente de cada ocurrencia) 0, 1 ó 2.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-

3-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 2-hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2- hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo C-enlazado, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y opcionalmente 1 ó 2 heteroátomos adicionales de anillo, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un grupo metilo, etilo o isopropilo y/o en 1 ó 2 átomos de carbono disponibles por un grupo metilo, etilo o fluoro;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, que contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3;

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de metilo y halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)- y en donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; o

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, bicíclico, de 6-10 miembros, que contiene opcionalmente 1 átomo de nitrógeno adicional (aparte del átomo N enlazante), en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)-.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, 1,3-difluoroprop-2-ilo, 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo y tetrahidrofurilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente, como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido, como se define anteriormente;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido como se define anteriormente;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido como se define anteriormente;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo o pirrolidinilo.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo,

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente en carbono o nitrógeno con un grupo metilo o etilo; HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y tienilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo;

HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo, piridilo, isoxazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo y/o (en un átomo de carbono) por fluoro;

HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es -$CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo o pirrolidinilo.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo, piridilo, isoxazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo y/o (en un átomo de carbono) por fluoro;

HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es metilo, fluoro o cloro;

R^2 es -$CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, 7-azabiciclo[2.2.1]hept-7-ilo, morfolino, o pirrolidinilo.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo, piridilo, isoxazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo y/o (en un átomo de carbono) por fluoro;

HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es metilo, fluoro o cloro;

R^2 es -$CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo o pirrolidinilo.

En otro aspecto de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;
HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo, piridilo, isoxazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente en un átomo de nitrógeno con metilo, difluorometilo, isopropilo o etilo y/o en un átomo de carbono por fluoro o metilo; siempre que cuando HET-1 es pirazolilo, R^1 se seleccione de 1-metoxiprop-2-ilo, isopropilo, y tetrahidrofurilo;
HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;
R^3 es metilo, fluoro o cloro;
R^2 es $-CONR^4R^5$ o $-SO_2NR^4R^5$, particularmente $-CONR^4R^5$;
R^4 y R^5 juntos forman un anillo azetidinilo, 7-azabiciclo[2.2.1]hept-7-ilo, morfolino, o pirrolidinilo.

En otro aspecto, Aspecto A, de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:
R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;
HET-1 se selecciona de pirazinilo (sustituido opcionalmente con metilo), pirazolilo ((sustituido opcionalmente en carbón por metilo), metiltiadiazolilo (particularmente 3-metil-1,2,4-tiadiazol-5-ilo), tiazolilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro) e isoxazolilo; siempre que cuando HET-1 es pirazolilo, particularmente R^1 se seleccione de 1-metoxiprop-2-ilo, isopropilo, y tetrahidrofurilo;
HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;
R^3 es metilo, fluoro o cloro;
R^2 es $-CONR^4R^5$ o $-SO_2NR^4R^5$, particularmente $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, 7-azabiciclo[2.2.1]hept-7-ilo, morfolino, o pirrolidinilo.

En otro aspecto, Aspecto B, de la invención se provee un compuesto de fórmula (I) o (IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de pirazinilo (sustituido opcionalmente con metilo), pirazolilo (sustituido opcionalmente en carbono por metilo), metiltiadiazolilo (particularmente 3-metil-1,2,4-tiadiazol-5-ilo), tiazolilo (sustituido opcionalmente con metilo), piridilo (sustituido opcionalmente por fluoro) e isoxazolilo; siempre que cuando HET-1 es pirazolilo, particularmente R^1 se seleccione de 1-metoxiprop-2-ilo, isopropilo, y tetrahidrofurilo;

HET-2 se selecciona de piridilo y pirazinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es metilo, fluoro o cloro;

R^2 es $-CONR^4R^5$ o $-SO_2NR^4R^5$, particularmente $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo o pirrolidinilo, particularmente azetidinilo.

Compuestos particulares de Aspecto B son aquellos de fórmulas (IB), (IC) y/o (ID).

En otro aspecto, Aspecto C, de la invención se provee un compuesto de fórmula (IB), (IC) o (ID) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1-hidroxiprop-2-ilo, tetrahidrofurilo y 1-metoxiprop-2-ilo; (particularmente R^1 se selecciona de isopropilo, (2S)-1-hidroxiprop-2-ilo, tetrahidrofuril y (2S)-1-metoxiprop-2-ilo);

HET-1 es metilpirazinilo;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo.

En otro aspecto, Aspecto D, de la invención se provee un compuesto de fórmula (IB) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1-hidroxiprop-2-ilo, tetrahidrofurilo y 1-metoxiprop-2-ilo; (particularmente R^1 se selecciona de isopropilo, (2S)-1-hidroxiprop-2-ilo, tetrahidrofurilo y (2S)-1-metoxiprop-2-ilo);

HET-1 es metilpirazinilo;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo.

En otro aspecto, Aspecto E, de la invención se provee un compuesto de fórmula (IB), (IC) o (ID) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, tetrahidrofurilo y 1-metoxiprop-2-ilo (particularmente (2S)-1-metoxiprop-2-ilo);

HET-1 es pirazolilo;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo.

En otro aspecto, Aspecto F, de la invención se provee un compuesto de fórmula (IB) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, tetrahidrofurilo y 1-metoxiprop-2-ilo (particularmente (2S)-1-metoxiprop-2-ilo);

HET-1 es pirazolilo;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, but-2-ilo, 1,3-difluoroprop-2-ilo, 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo y tetrahidrofurilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

R^2 es $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, 1-hidroxiprop-2-ilo y 1-metoxiprop-2-ilo, HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente en carbono o nitrógeno con un grupo metilo o etilo;

HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y tienilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

R^2 es $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo; HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de isopropilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo;

HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-CONR^4R^5$ o $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En un aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente en carbono o nitrógeno con un grupo metilo etilo;

HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y tienilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-CONR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En un aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

HET-2 es un anillo heteroarilo, de 5 ó 6 miembros, sustituido opcionalmente como se define anteriormente;

R^2 es $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

En otro aspecto de la invención se provee un compuesto de fórmula (I) (o IA) como se define anteriormente, o su sal, en donde:

R^1 se selecciona de 1-fluorometoxiprop-2-ilo y 1,1-difluorometoxiprop-2-ilo;

HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente en carbono o nitrógeno con un grupo metilo etilo;

HET-2 se selecciona de piridilo, pirazinilo, tiazolilo y tienilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es fluoro o cloro;

R^2 es $-SO_2NR^4R^5$;

R^4 y R^5 juntos forman un anillo azetidinilo, pirrolidinilo o morfolino.

Otros compuestos preferidos de la invención son cada uno de los Ejemplos (y sus sales), cada uno de los cuales provee un aspecto adicional independiente de la invención. En otros aspectos, la presente invención comprende igualmente cualesquiera dos o más compuestos de los Ejemplos (y sus sales).

Compuestos particulares de la invención uno cualquiera o más de:

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-1,3-tiazol-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-1,3-tiazol-2-ilbenzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-1,3-tiazol-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H- pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H- pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[5-(azetidin-1-ilsulfonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil] oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[3-cloro-5-(morfolin-4-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida; y
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida; y/o
3-{[5-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metilpropil] oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metilpropil] oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[2-(azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[2-(azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[2-fluoro-1-(fluorometil) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il] oxi}-5-{[2-fluoro-1-(fluorometil) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-({(1S)-2-[(difluorometil)oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il) benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il) benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1R,2R)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S,2S)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[4-(azetidin-1-ilcarbonil)- 1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[4-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-[(1-metiletil) oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-(hidroximetil) propil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida; y/o
3-{[2-(azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-(ciclopentiloxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5 -(ciclopentiloxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-(ciclopentiloxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1R,2R)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S,2S)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[4-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-5-[(1-metiletil) oxi]-N-(5-metilpirazin-2-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1,3-tiazol-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-piridin-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(1-metiletil)oxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(1-metiletil)oxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(1-metiletil)oxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-piridin-2-ilbenzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-isoxazol-3-il-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil) oxi]-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-1H-pirazol-3-ilbenzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil) oxi]-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1,5-dimetil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1,5-dimetil-1H-pirazol-3-il)-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridazin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(4-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-1H-pirazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1,5-dimetil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(4-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(5-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-1H-pirazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-metilpirazin-2-il)-5 -[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-fluoropiridin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[3-cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;

3-{[5-cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[3-cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida; y
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3R)-tetrahidrofuran-3-iloxi]benzamida; y/o
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-isoxazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-pirazin-2-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-fluoropiridin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-piridin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-isoxazol-3-il-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(4-metil-1,3-tiazol-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metil-1,3-tiazol-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-pirazin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-pirazin-2-ilbenzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-pirazin-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil) oxi]-N-pirazin-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-pirazin-2-ilbenzamida;

3-{[3-cloro-5-(morfolin-4-ilcarbonil)piridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(7-azabiciclo[2.2.1]hept-7-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-metil-1H- pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida; y

3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida; y/o

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi} -5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-pirazin-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-piridin-2-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

N-(1-metil-1H-pirazol-3-il)-3-{[6-(pirrolidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-pirazin-2-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il] oxi}-N-1H-pirazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(5-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil) etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil] oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilsulfonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-[1-(difluorometil)-1H-pirazol-3-il]-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-[1-(difluorometil)-1H-pirazol-3-il]-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-[1-(difluorometil)-1H-pirazol-3-il]-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida; y/o
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1R)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
o su sal.

Una característica adicional de la invención es una composición farmacéutica que comprende un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) como ya se definió, o su sal farmacéuticamente aceptable, junto con un diluyente o vehículo farmacéuticamente aceptable.

De acuerdo con otro aspecto de la invención se provee un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o una sal farmacéuticamente aceptable como ya se definió, para uso como un medicamento.

De acuerdo con otro aspecto de la invención se provee un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable como se define anteriormente para uso como un medicamento para el tratamiento de una enfermedad medida por GLK, en particular diabetes tipo 2.

Además, de acuerdo con la invención se provee el uso de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable en la preparación de un medicamento para tratamiento de una enfermedad mediada por GLK, en particular diabetes tipo 2.

El compuesto se formula adecuadamente como una composición farmacéutica para uso en esta forma.

De acuerdo con otro aspecto de la presente invención se provee un método de tratar enfermedades mediadas por GLK, especialmente diabetes, administrando una cantidad efectiva de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable, a un mamífero necesitado de dicho tratamiento.

Enfermedades específicas que pueden tratarse por un compuesto o composición de la invención incluyen: disminución de glucosa sanguínea en Diabetes Mellitus tipo 2 con un serio riesgo de hipoglicemia (y potencial para tratar tipo 1), dislipidemia, obesidad, resistencia a la insulina, síndrome X metabólico, tolerancia anormal a la glucosa.

Como ya se discutió, el sistema GLK/GLKRP puede describirse como un potencial objetivo "Diabesity" (benéfico para combatir la Diabetes y en la Obesidad). En consecuencia, de acuerdo con otro aspecto de la invención se provee el uso de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable, en la preparación de un medicamento para uso en el tratamiento combinado o prevención, particularmente tratamiento de diabetes y obesidad.

De acuerdo con otro aspecto de la invención se provee el uso de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable, en la preparación de un medicamento para uso en el tratamiento o prevención, particularmente tratamiento de obesidad.

De acuerdo con otro aspecto de la invención se provee un compuesto de fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable como se define anteriormente para uso como un medicamento para el tratamiento o prevención, particularmente el tratamiento de obesidad.

De acuerdo con un aspecto adicional de la invención se provee un método para el tratamiento combinado de obesidad y diabetes administrando una cantidad efectiva de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable, a un mamífero necesitado de dicho tratamiento.

De acuerdo con un aspecto adicional de la invención se provee un método para el tratamiento de obesidad administrando una cantidad efectiva de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID) o su sal farmacéuticamente aceptable, a un mamífero necesitado de dicho tratamiento.

Los compuestos de la invención pueden ser particularmente apropiados para uso como productos farmacéuticos, debido a propiedades físicas y/o farmacocinéticas, y/o perfil de toxicidad favorable y/o perfil metabólico favorable.

El perfil de toxicidad favorable puede demostrarse, por ejemplo, mediante el uso del análisis de la prueba de Ames, y/o mediante experimentación contra el canal de iones hERG. Un perfil metabólico favorable puede significar, por ejemplo, una tasa reducida de metabolismo, que lleva a la disminución en la depuración del compuesto del organismo y, por consiguiente, mayor exposición al compuesto, o un perfil metabólico favorable puede significar, por ejemplo, no formar metabolitos activos (que podrían considerarse indeseables en algunas circunstancias).

Por ejemplo, los compuestos de los Aspectos A a F pueden tener perfiles toxicológicos favorables.

Las composiciones de la invención pueden estar en una forma apropiada para uso oral (por ejemplo como tabletas, pastillas para chupar, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos dispersables o gránulos, jarabes o elíxires), para uso tópico (por ejemplo como cremas, ungüentos, geles, o soluciones acuosas u oleosas o suspensiones), para administración por inhalación (por ejemplo como un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo como un polvo finamente dividido) o para administración parenteral (por ejemplo como una solución estéril acuosa u oleosa para medicación intravenosa, subcutánea, intramuscular o como un supositorio para medicación rectal). Se prefieren presentaciones farmacéuticas apropiadas para uso oral.

Las composiciones de la invención pueden obtenerse por procedimientos convencionales usando excipientes farmacéuticos convencionales, bien conocidos en el arte. Por lo tanto, las composiciones destinadas a uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o preservantes.

Excipientes apropiados, farmacéuticamente aceptables, para una formulación de tableta incluyen, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y desagregantes tales como almidón de maíz o ácido algénico; agentes aglutinantes tales como almidón; agentes lubricantes tales como estearato de magnesio, ácido esteárico o talco; agentes preservantes tales como p-hidroxibenzoato de propilo o etilo, y anti-oxidantes, tales como ácido ascórbico. Las formulaciones de tableta pueden ser recubiertas o no recubiertas ya sea para modificar su desagregación y la subsiguiente absorción del ingrediente activo en el tubo digestivo, o ya sea para mejorar su estabilidad y/o apariencia, en cualquiera de los dos casos, usando agentes de recubrimiento convencionales y procedimientos bien conocidos en el arte.

Composiciones para uso oral pueden estar en la forma de cápsulas de gelatina duras, en las cuales el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blandas en las cuales el ingrediente activo se mezcla con agua o un aceite tal como aceite de maní, parafina líquida o aceite de oliva.

Las suspensiones acuosas contienen por lo general el ingrediente activo en forma finamente pulverizada junto con uno o más agentes de suspensión, tales como carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes dispersantes o humectantes tales como lecitina o productos de la condensación de un óxido de alquileno con ácidos grasos (por ejemplo polioxetilen estearato), o productos de la condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de la condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietilen sorbitol, o productos de la condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetileneoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de polietilen sorbitán. Las suspensiones acuosas pueden contener igualmente uno o más preservantes (tales como p-hidroxibenzoato de propilo o etilo, anti-oxidantes (tales como ácido ascórbico), agentes colorantes, agentes saborizantes, y/o agentes edulcorantes (tales como sacarosa, sacarina o aspartame).

Suspensiones oleosas pueden formularse suspendiendo el ingrediente activo en un aceite vegetal (tales como aceite de maní, aceite de oliva, aceite de ajonjolí o aceite de coco) o en un aceite mineral (tal como parfina líquida). Las suspensiones oleosas pueden contener asimismo un agente espesante tal como cera de abejas, parafina dura o alcohol cetílico. Agentes edulcorantes tales como los ya expuestos, y agentes saborizantes pueden agregarse para proporcionar una preparación oral agradable. Estas

composiciones pueden preservarse por la adición de un anti-oxidante tal como ácido ascórbico.

Agentes y gránulos dispersables apropiados para la preparación de una suspensión acuosa mediante la adición de agua generalmente contienen el ingrediente activo junto con un agente dispersante o humectante, un agente de suspensión y uno o más preservantes. Agentes dispersantes o humectantes adecuados y agentes de suspensión se ejemplifican por aquellos ya mencionados más arriba en el texto. De la misma forma pueden estar presentes otros excipientes, por ejemplo agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención pueden estar igualmente en la forma de emulsiones aceite-en-agua. La fase oleosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de maní, o un aceite mineral, tal como por ejemplo parafina líquida una mezcla de de cualquiera de éstos. Agentes emulsificantes apropiados pueden ser, por ejemplo, gomas de ocurrencia natural tales como goma acacia o goma tragacanto, fosfatados de ocurrencia natural tales como fríjol de soya, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejemplo monooleato de sorbitano) y productos de la condensación de dichos ésteres parciales con óxido de etileno tales como monooleato de polioxietilen sorbitano. Del mismo modo las emulsiones pueden contener agentes edulcorantes, saborizantes y preservantes.

Jarabes y elíxires pueden formularse con agentes edulcorantes tales como glicerol, propilen glicol, sorbitol, aspartame o sacarosa, y pueden contener también un agente emoliente, preservante, saborizante y/o colorante.

Las composiciones farmacéuticas pueden estar asimismo en la forma de una suspensión oleosa o acuosa inyectable estérilo, la cual puede formularse de acuerdo con procedimientos conocidos usando uno o más de los agentes humectantes o dispersantes apropiados y agentes de suspensión, que ya han sido mencionados. Una preparación inyectable estéril puede también una solución o suspensión inyectable estéril en un diluyente o

disolvente parenteralmente aceptable, no tóxico, por ejemplo una solución en 1,3-butanodiol.

Composiciones para administración por inhalación pueden estar en la forma de un aerosol presurizado convencional dispuesto para dispensar el ingrediente activo, ya sea como un aerosol que contiene gotículas de sólido o líquido finamente dividido. Pueden utilizarse propulsores de aerosol convencionales tales como hidrocarburos fluorados volátiles o hidrocarburos y el dispositivo aerosol se dispone convenientemente para dispensar una cantidad medida de ingrediente activo.

Para mayor información sobre la formulación, se remite al lector al Capítulo 25.2 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una forma farmacéutica única dependerá necesariamente del anfitrión tratado y de la vía particular de administración. Por ejemplo, una formulación destinada para administración oral a humanos contendrá generalmente, por ejemplo, desde 0.5 mg a 2 g de agente activo combinado con una cantidad conveniente y apropiada de excipientes que puede variar desde alrededor de 5 a alrededor de 98 por ciento en peso de la composición total. Presentaciones farmacéuticas unitarias contendrán por lo general alrededor de 1 mg a alrededor de 500 mg de un ingrediente activo. Para mayor información sobre Rutas de Administración y Regímenes Farmacéuticos se remite al lector al Capítulo 25.3 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

El tamaño de la dosis para efectos terapéuticos o profilácticos de un compuesto de la fórmula (I), (IA), (IB), (IC) o (ID) variará naturalmente de acuerdo con la naturaleza y gravedad de las enfermedades, la edad y el sexo del paciente o animal y la vía de administración, de acuerdo principios bien conocidos de la medicina.

Cuando se emplea un compuesto de la fórmula (I), (IA), (IB), (IC) o (ID) con propósitos terapéuticos o profilácticos se administrará

generalmente de modo que se reciba una dosis diaria en el rango de, por ejemplo, 0.5 mg a 75 mg por kg de peso corporal, administrada, si se requiere, en dosis divididas. En general, se administrarán dosis menores cuando se emplea una vía parenteral. Así, por ejemplo, para administración intravenosa, se usará generalmente una dosis en el rango de, por ejemplo, 0.5 mg a 30 mg por kg de peso corporal. De manera similar, para administración por inhalación, se utilizará una dosis en el rango de, por ejemplo, 0.5 mg a 25 mg por kg de peso corporal. No obstante, se prefiere la administración oral.

La elevación de la actividad GLK descrita aquí puede aplicarse como terapia única o en combinación con una o más sustancias diferentes y/o tratamientos para la indicación que se está tratando. Tal tratamiento conjunto puede lograrse mediante la administración simultánea, secuencial o separada de los componentes individuales del tratamiento. El tratamiento simultáneo puede ser en una tableta única o en tabletas separadas. Por ejemplo en el tratamiento de diabetes mellitus, la quimioterapia puede incluir las siguientes categorías principales de tratamiento:

1) Insulina y análogos de insulina;

2) Secretagogos de insulina incluidas sulfonilureas (por ejemplo glibenclamida, glipizida), reguladores de glucosa prandial (por ejemplo repaglinida, nateglinida);

3) Agentes que mejoran la acción de la incretina (por ejemplo inhibidores de dipeptidil peptidasa IV, y agonistas de GLP-1);

4) Agentes sensibilizantes a la insulina incluidos agonistas PPARgamma (por ejemplo pioglitazona y rosiglitazona), y agentes con actividad combinada PPAR α y γ;

5) Agentes que modulan el balance de glucosa hepática (por ejemplo metformina, inhibidores de fructosa 1,6 bisfosfatasa, inhibidores de glucógeno fosforilasa, inhibidores de glucógeno sintasa cinasa);

6) Agentes diseñados para reducir la absorción de glucosa del intestino (por ejemplo acarbosa);

7) Agentes que evitan la reabsorción de glucosa por el riñón (inhibidores de SGLT);

8) Agentes diseñados para tratar las complicaciones de hiperglucemia prolongada (por ejemplo inhibidores de aldosa reductasa);

9) Agentes anti-obesidad (por ejemplo sibutramina y orlistat);

10) Agentes anti-dislipidemia tales como inhibidores de HMG-CoA reductasa (por ejemplo, estatinas); agonistas de PPARα (fibratos, por ejemplo gemfibrozil); reductores de ácido biliar (colestiramina); inhibidores de absorción del colesterol (estanoles vegetales, inhibidores sintéticos); inhibidores de absorción de ácido biliar (IBATi) y ácido nicotínico y análogos (niacina y formulaciones de liberación lenta);

11) Agentes antihipertensores tales como, bloqueadores β (por ejemplo atenolol, inderal); inhibidores de ACE (por ejemplo lisinopril); antagonistas de calcio (por ejemplo nifedipina); antagonistas de receptor de angiotensina (por ejemplo candesartán), antagonistas α y agentes diuréticos (por ejemplo furosemida, benztiazida);

12) Moduladores de hemostasis tales como, antitrombóticos, activatores de fibrinólisis y agentes antiplaquetarios; antagonistas de trombina; inhibidores de factor Xa; inhibidores de factor VIIa); agentes antiplaquetarios (por ejemplo aspirina, clopidogrel); anticoagulantes (heparina y análogos de bajo peso molecular, hirudina) y warfarina;

13) Agentes que antagonizan las acciones del glucagón; y

14) Agentes anti-inflamatorios, tales como medicamentos anti-inflamatorios no esteroideos (por ejemplo aspirina) y agentes anti-inflamatorios esteroideos (por ejemplo cortisona).

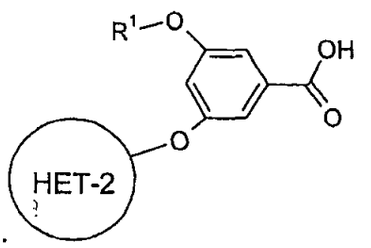
De acuerdo con otro aspecto de la presente invención se proveen compuestos individuales producidos como productos finales en los Ejemplos expuestos, y sus sales.

Un compuesto de la invención, o su sal, puede prepararse por cualquier proceso conocido por ser aplicable a la preparación de tales compuestos o compuestos estructuralmente relacionados. Grupos funcionales pueden protegerse y desprotegerse usando métodos

convencionales. Para ejemplos de grupos protectores tales como grupos protectores amino y ácido carboxílico (así como medios de formación y desprotección eventual), véase T.W. Greene y P.G.M. Wuts, "Protective Groups in Organic Synthesis", Second Edition, John Wiley & Sons, New York, 1991.

Procesos para la síntesis de Compuestos de Fórmula (I), (IA), (IB), (IC) o (ID) se proveen como una característica adicional de la invención. Por consiguiente, de acuerdo con un aspecto adicional de la invención se provee un proceso para la preparación de un compuesto de Fórmula (I), (IA), (IB), (IC) o (ID), que comprende un proceso a) a e) (en donde las variables son como se definen más arriba en el texto para Compuestos de Fórmula (I), (IA), (IB), (IC) o (ID) a menos que se defina lo contrario):

(a) Reacción de un ácido de Fórmula (III) o su derivado activado con un compuesto de Fórmula (IV), en donde R^1 es como se define anteriormente o su versión protegida;



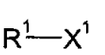
(III)



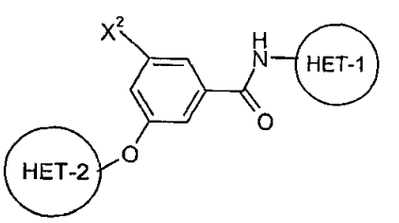
(IV);

o

(b) reacción de un compuesto de Fórmula (V) con un compuesto de Fórmula(VI),



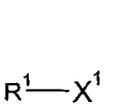
(V)



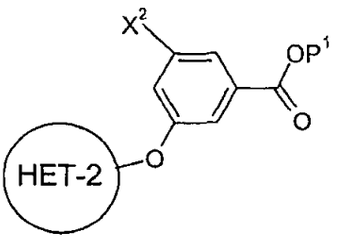
(VI)

en donde X^1 es un grupo saliente y X^2 es un grupo hidroxilo o X^1 es un grupo hidroxilo y X^2 es un grupo saliente, y en donde R^1 es como se define anteriormente o su versión protegida;

proceso (b) podría llevarse igualmente usando el éster intermedio de Fórmula (VII), en donde P^1 es un grupo protector como de describe más adelante, seguido por hidrólisis del éster y formación de amida mediante procedimientos descritos en alguna otra parte y bien conocidos por los expertos en el arte;



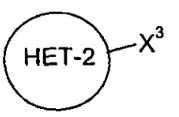
(V)



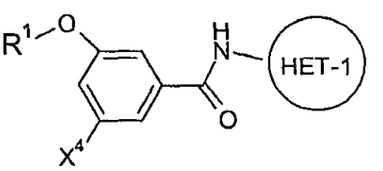
(VII)

o

(c) reacción de un compuesto de Fórmula (VIII) con un compuesto de Fórmula (IX)



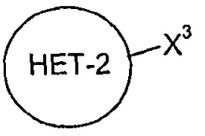
(VIII)



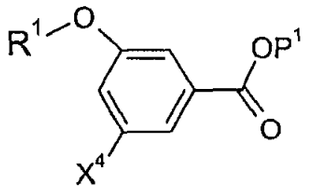
(IX)

en donde X^3 es un grupo saliente o un reactivo organometálico y X^4 es un grupo hidroxilo o X^3 es un grupo hidroxilo y X^4 es un grupo saliente o un reactivo organometálico, y en donde R^1 es como se define anteriormente o su versión protegida;

proceso (c) podría llevarse también a cabo usando el éster intermedio de Fórmula (X), seguido por hidrólisis de éster y formación de amida por procedimientos descritos en alguna otra parte y bien conocidos por los expertos en el arte;

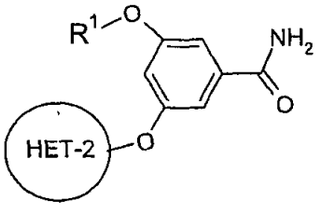


(VIII)



(X)

(d) reacción de un compuesto de Fórmula (XI) con un compuesto de Fórmula (XII),



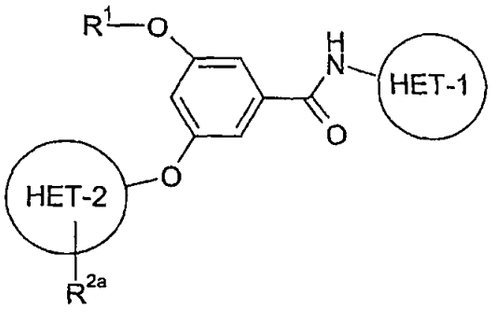
(XI)



(XII);

en donde X^5 es un grupo saliente; y en donde R^1 es como se define anteriormente o su versión protegida; o

e) reacción de un compuesto de fórmula (XIII)



(XIII)

en donde R^{2a} es un precursor de R^2, tal como ácido carboxílico, éster o anhídrido (para R^2 = -$CONR^4R^5$) o los equivalentes de ácido sulfónico (para R^2 es -$SO^2NR^4R^5$); con una amina de fórmula -NR^4R^5;

y, posteriormente, si es necesario:

i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

ii) retirar cualesquiera grupos protectores; y/o

iii) formar una sal del mismo.

Números salientes apropiados X^1 a X^5 para los procesos b) a d) son cualquier grupo saliente conocido en el arte para estos tipos de reacciones, por ejemplo halo, alcoxi, trifluorometanosulfoniloxi, metanosulfoniloxi, o

p-toulenosulfoniloxi; o un grupo (tal como un grupo hidroxi) que puede convertirse en un grupo saliente (tal como un grupo oxitrifenilfosfonio) *in situ*.

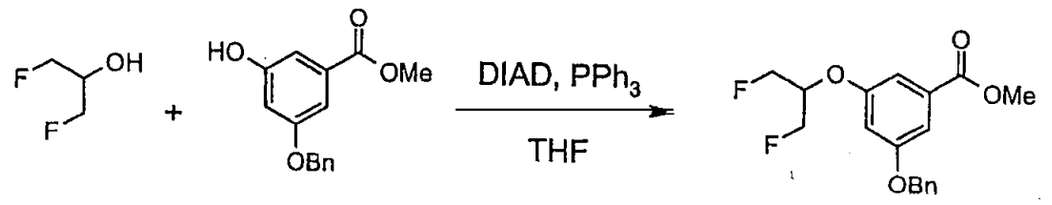
Valores apropiados para R^1 que contienen un grupo hidroxi protegido son cualquier grupo hidroxi protegido apropiado conocido en el arte, por ejemplo éteres simples tales como un metil éter, *terc*-butil éter o silil éteres tales como -OSi[(1-4C)alquil]$_3$ (en donde cada grupo (1-4C)alquilo se selecciona independientemente de metilo, etilo, propilo, isopropilo, y tertbutilo. Ejemplos de tales grupos trialquilsililo son trimetilsililo, trietilsililo, triisopropilsililo y *terc*-butildimetilsililo. Silil éteres adicionales apropiados son aquellos que contienen fenilo y grupos fenilo sustituido, tales como -Si(PhMe$_2$) y -Si(TolMe$_2$) (en donde Tol = metilbenceno). Otros valores apropiados para grupos protectores hidroxi se relacionan más adelante.

Compuestos de Fórmulas (III) a (XII) se pueden obtener en el comercio, o son conocidos en el arte, o pueden elaborarse por procesos conocidos en el arte, por ejemplo, como se muestra en los Ejemplos acompañantes, o se describe a continuación. Para mayor información sobre procesos para elaborar tales compuestos, nos referimos a nuestras publicaciones PCT WO 03/000267, WO 03/015774 y WO 03/000262 y sus referencias en ellas. En general, se observará que cualquier enlace aril-O o alquil-O puede formarse por sustitución nucleófila o procesos catalizados por metal, opcionalmente en la presencia de una base apropiada.

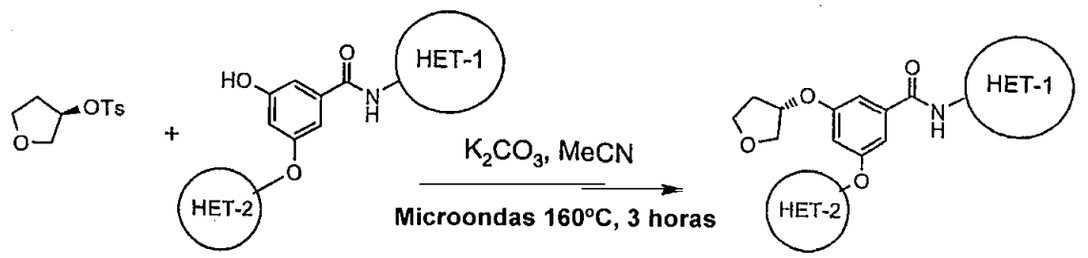
Compuestos de fórmula (XIII) pueden elaborarse por procesos tales como los mostrados en procesos a) a d) y/o por aquellos procesos ya mencionados para compuestos de fórmulas (III) a (XII).

El grupo R^1 en los compuestos de fórmulas (III), (IX), (X), (XI) y (XIII) pueden elaborarse mediante reacción de precursores apropiados con compuestos de fórmula (V) o sus derivados, dependiendo de la naturaleza del grupo R^1, por ejemplo, mediante desplazamiento nucleófilo de un grupo saliente X^1 en un compuesto de fórmula (V). Por lo general, los compuestos de fórmula (V) se encuentran disponibles en el comercio o

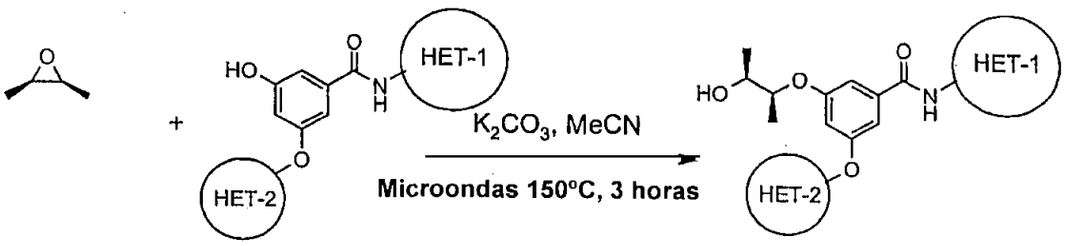
pueden elaborarse mediante sencillas interconversiones de grupos funcionales a partir de compuestos disponibles en el comercio, o mediante métodos de la literatura. Mayor información se encuentra en WO2004/076420, WO2005/054200, WO2005/054233, WO 2005/044801 y WO 2005/056530. Algunos ejemplos ilustrativos usando varios grupos R^1 se dan en los Esquemas siguientes, y/o en los ejemplos acompañantes, y generalmente pueden aplicarse en forma análoga a grupos R^1 no mostrados más adelante por métodos conocidos en el arte; véase por ejemplo Bull. Chem. Soc. Japan, 73 (2000), 471-484, Solicitud Internacional de Patente WO 2002/050003 y Bioorganic and Medicinal Chemistry Letters, (2001), *11*, 407.



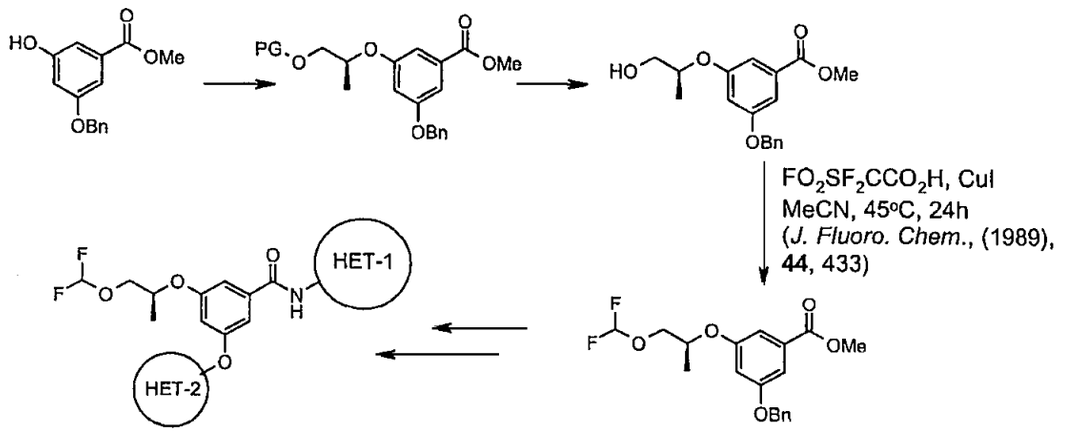
Esquema 1



Esquema 2



Esquema 3



Esquema 4

[PG es un grupo protector, Ts es p-toluenosulfonilo].

Ejemplos de conversiones de un compuesto de fórmula (I) en otro compuesto de fórmula (I), bien conocidas por los expertos en el arte, incluyen interconversiones de grupos funcionales tales como hidrólisis, hidrogenación, hidrogenólisis, oxidación o reducción, y/o funcionalización adicional mediante reacciones estándar tales como acoplamiento catalizado por amida o por metal, reacciones de desplazamiento nucleófilo. Ejemplos adicionales de una conversión de un compuesto de fórmula (I) en otro compuesto de fórmula (I) es la metilación de un grupo hidroxi en R^1 para producir un grupo metoxi, y conversión, por ejemplo, de un grupo hidroximetilo en R^1 (tal como cuando R^1 es hidroxiprop-2-ilo) en un grupo difluorometoxi, utilizando reacciones tales como las ilustradas en el Esquema 4.

Se entenderá que los sustituyentes R^3, R^6 y/o R^7 pueden introducirse en la molécula en cualquier punto conveniente en la secuencia sintética, o pueden estar presentes en los materiales de partida. Un precursor de uno de estos sustituyentes puede estar presente en la molécula durante los pasos del proceso a) a e) ya indicados, y transformarse luego en el sustituyente deseado como paso final para formar el compuesto de fórmula (I); seguido, donde sea necesario, por

i) convertir un compuesto de fórmula (I) en otro compuesto de fórmula (I);

ii) retirar cualesquiera grupos protectores; y/o

iii) formar una sal del mismo.

Condiciones de reacción específicas para las reacciones mencionadas son las siguientes, en donde cuando P^1 es un grupo protector, P^1 es preferiblemente (1-4C)alquilo, por ejemplo metilo o etilo:

Proceso a) – reacciones de acoplamiento de grupos amino con ácidos carboxílicos para formar una amida son bien conocidos en el arte. Por ejemplo,

(i) usando una reacción de acoplamiento apropiada, tal como una reacción de acoplamiento de carbodiimida realizada con EDAC (1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato) en la presencia de dimetilaminopiridina (DMAP) en un disolvente apropiado tal como diclorometano (DCM), cloroformo o dimetilformamida (DMF) a temperatura de la sala; o

(ii) reacción en la cual el grupo carboxílico se activa en un cloruro ácido mediante reacción con cloruro de oxalilo en la presencia de un disolvente apropiado tal como DCM. El cloruro ácido puede hacerse reaccionar entonces con un compuesto de Fórmula (IV) en la presencia de una base, tal como trietilamina o piridina, en un disolvente apropiado tal como cloroformo o DCM a una temperatura entre 0°C y 80°C.

Proceso b) - Compuestos de Fórmulas (V) y (VI) pueden hacerse reaccionar juntos en un disolvente apropiado, tal como DMF o tetrahidrofurano (THF), con una base tal como hidruro de sodio o *terc*-butóxido de potasio, a una temperatura en el rango 0 a 200°C, opcionalmente usando calentamiento con microondas o catálisis de metal tal como acetato de paladio (II), paladio sobre carbón, acetato de cobre (II) o yoduro de cobre (I); alternativamente, Compuestos de Fórmulas (V) y (VI) pueden hacerse reaccionar juntos en un disolvente apropiado, tal como THF o DCM, con una fosfina adecuada tal como trifenilfosfina, y azodicarboxilato tal como dietilazodicarboxilato; proceso b) podría llevarse a cabo también usando un precursor al éster de fórmula (VII) tal como un arilo-nitrilo o derivado de trifluorometilo, seguido por conversión en un ácido carboxílico y formación de amida como se describe previamente;

Proceso c) - Compuestos de Fórmulas (VIII) y (IX) pueden hacerse reaccionar juntos en un disolvente apropiado, tal como DMF o THF, con una base tal como hidruro de sodio o *terc*-butóxido de potasio, a una temperatura en el rango 0 a 200°C, opcionalmente usando calentamiento con microondas o catálisis de metal tal como acetato de paladio (II), paladio sobre carbón, acetato de cobro (II) o yoduro de cobre (I); proceso c) podría llevarse asimismo a cabo usando un precursor al éster de fórmula (X) tal como un arilo-nitrilo o un derivado de trifluorometilo, seguido por conversión en un ácido carboxílico y formación de amida como se describe previamente.

Los compuestos de la fórmula (VIII) se encuentran disponibles en el comercio o pueden prepararse de materiales disponibles en el comercio mediante procesos bien conocidos en el arte, por ejemplo interconversiones de grupos funcionales (tales como hidrólisis, hidrogenación, hidrogenólisis, oxidación o reducción), y/o funcionalización adicional y/o ciclación mediante reacciones estándar (tales como acoplamiento catalizado por amida o sulfonamida o metal, o reacciones de desplazamiento nucleófilo o electrófilo);

Proceso d) - reacción de un compuesto de Fórmula (XI) con un compuesto de Fórmula (XII) puede realizarse en un disolvente polar, tal como DMF o un disolvente no polar tal como THF con una base fuerte, tal como hidruro de sodio o *terc*-butóxido de potasio a una temperatura entre 0 y 200°C, opcionalmente usando calentamiento con microondas o catálisis de metal, tal como acetato de paladio (II), paladio sobre carbón, acetato de cobre (II) o yoduro de cobre (I).

Proceso e) – reacciones de acoplamiento de grupos amino con ácidos carboxílico o sulfónico o derivados de ácido para formar una amida son bien conocidas en el arte y se describen anteriormente para el Proceso a).

Se considera que ciertos intermedios de fórmula (III), (VI), (VII), (IX) y/o (XI) son novedosos y comprenden un aspecto independiente de la invención.

Se considera que ciertos intermedios de fórmula (III), (IX) y/o (XI), en donde R^1 es como se define en esta solicitud para un compuesto de fórmula (I), son novedosos y comprenden un aspecto independiente de la invención.

Se considera que ciertos intermedios de fórmula (XIII) son novedosos y comprenden un aspecto independiente de la invención.

Durante el proceso de preparación, puede ser ventajoso utilizar un grupo protector para un grupo funcional en la molécula. Grupos protectores pueden retirarse por cualquier método convencional como se describe en la literatura o conocido por el químico experto, según lo apropiado, para el retiro del grupo protector en cuestión, seleccionándose tales métodos con el fin de efectuar el retiro del grupo protector con alteración mínima de grupos en alguna otra parte en la molécula.

Ejemplos específicos de grupos protectores se consignan más adelante por razones de conveniencia, en los cuales "inferior" significa que el grupo al cual se aplica preferiblemente tienen 1-4 átomos de carbono. Se entenderá que estos ejemplos no son exhaustivos. Donde, más adelante, se dan ejemplos específicos de métodos para el retiro de grupos protectores, éstos análogamente no son exhaustivos. El uso de grupos protectores y métodos de desprotección no específicamente mencionados se encuentra, naturalmente, dentro del ámbito de la invención.

Un grupo protector carboxi puede ser el residuo de un alcohol alifático o aralifático formador de éster o de un silanol formador de éster (conteniendo preferiblemente dicho alcohol o silanol 1-20 átomos de carbono). Ejemplos de grupos protectores carboxi incluyen grupos (1-12C)alquilo de cadena recta o ramificada (por ejemplo isopropilo, *t*-butilo); grupos alquilo inferior alcoxi inferior (por ejemplo metoximetilo, etoximetilo, isobutoximetilo; grupos alquilo inferior aciloxi alifático inferior, (por ejemplo acetoximetilo, propioniloximetilo, butiriloximetilo, pivaloiloximetili); grupos alquilo inferior alcoxicarboniloxi inferior (por ejemplo 1-metoxicarboniloxietilo, 1-etoxicarboniloxietilo); grupos alquilo inferior arilo (por ejemplo p-metoxibencilo, o-nitrobencilo, p-nitrobencilo,

benzhidrilo y ftalidilo); grupos tri(alquilo inferior)sililo (por ejemplo trimetilsililo y *t*-butildimetilsililo); grupos alquilo inferior tri(alquilo inferior)sililo (por ejemplo trimetilsililetilo); y grupos (2-6C)alquenilo (por ejemplo alilo y viniletilo).

Métodos particularmente apropiados para el retiro de grupos protectores carboxilo incluyen por ejemplo hidrólisis catalizada por ácido, metal o enzimas. Asimismo, se puede emplear hidrogenación.

Ejemplos de grupos protectores hidroxi incluyen grupos metilo, *t*-butilo, alquenilo inferior (por ejemplo alilo); grupos alcanoilo inferior (por ejemplo acetilo); grupos alcoxicarbonilo inferior (por ejemplo t-butoxicarbonilo); grupos alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonili); grupos alcoxicarbonilo inferior arilo (por ejemplo benzoiloxicarbonilo, p-metoxibenciloxicarbonilo, o-nitrobenciloxicarbonilo, p-nitrobenciloxicarbonilo); grupos arilsililo/alquilo inferior (por ejemplo trimetilsililo, t-butildimetilsililo, t-butildifenilsililo); tetrahidropiran-2-ilo; grupos alquilo inferior arilo (por ejemplo bencilo); y grupos alquilo inferior triarilo (por ejemplo trifenilmetilo). Ejemplos de grupos protectores amino incluyen grupos formilo, aralquilo (por ejemplo bencilo y bencilo sustituido, por ejemplo p-metoxibencilo, nitrobencilo y 2,4-dimetoxibencilo, y trifenilmetilo); grupos di-p-anisilmetilo y furilmetilo; alcoxicarbonilo inferior (por ejemplo t-butoxicarbonilo); alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos alcoxicarbonilo inferior arilo (por ejemplo benciloxicarbonilo, p-metoxibenciloxicarbonilo, o-nitrobenciloxicarbonilo, p-nitrobenciloxicarbonilo; trialquilsililo (por ejemplo trimetilsililo y t-butildimetilsililo); grupos alquilideno (por ejemplo metilideno); bencilideno y bencilideno sustituido.

Métodos apropiados para retiro de grupos protectores hidroxi y amino incluyen, por ejemplo, hidrogenación, desplazamiento nucleófilo, hidrólisis catalizada por ácido, base, metal o enzimas, hidrogenólisis catalítica o fotolíticamente para grupos tales como o-nitrobenciloxicarbonilo, o con iones de fluoruro para grupos sililo. Por ejemplo, grupos protectores metil

éter para grupos hidroxi pueden retirarse mediante yoduro de trimetilsililo. Un grupo protector *terc*-butil éter para un grupo hidroxi puede retirarse mediante hidrólisis, por ejemplo utilizando ácido clorhídrico en metanol.

Ejemplos de grupos protectores para grupos amida incluyen aralcoximetilo (por ejemplo benciloximetilo y benciloximetilo sustituido); alcoximetilo (por ejemplo metoximetilo y trimetilsililetoximetilo); tri alquilo/arilsililo (por ejemplo trimetilsililo, t-butildimetilsililo, t-butildifenilsililo); tri alquil/arilsililoximetilo (por ejemplo t-butildimetilsililoximetilo, t-butildifenilsililoximetilo); 4-alcoxifenilo (por ejemplo 4-metoxifenilo); 2,4-di(alcoxi)fenilo (por ejemplo 2,4-dimetoxifenilo); 4-alcoxibencilo (por ejemplo 4-metoxibencilo); 2,4-di(alcoxi) bencilo (por ejemplo 2,4-di(metoxi)bencilo); y alqu-1-enilo (por ejemplo alilo, but-1-enilo y vinilo sustituido por ejemplo 2-fenilvinilo).

Grupos aralcoximetilo pueden introducirse en el grupo amida haciendo reaccionar el último grupo con el cloruro de aralcoximetilo apropiado, y retirarse por hidrogenación catalítica. Grupos alcoximetilo, tri alquilo/arilsililo y trialquilo/sililoximetilo pueden introducirse haciendo reaccionar la amida con el cloruro apropiado y retirando con ácido; o, en el caso de grupos que contienen sililo, iones de flúor. Los grupos alcoxifenilo y alcoxibencilo se introducen convenientemente por arilación o alquilación con un haluro apropiado y se retiran por oxidación con nitrato de amonio cérico. Finalmente, grupos alqu-1-enilo pueden introducirse haciendo reaccionar la amida con el aldehído apropiado y se retiran con ácido.

En lo anterior, se aplican asimismo otras características de la composición farmacéutica, proceso, método, uso y fabricación de medicamento, los aspectos e incorporaciones alternativas y preferidas de los compuestos de la invención, descritas en esta solicitud.

Los siguientes ejemplos son para efectos de ilustración y no tienen como finalidad limitar el ámbito de esta solicitud. Cada compuesto ejemplificado representa un aspecto particular e independiente de la invención. En los siguientes Ejemplos no limitantes, a menos que se especifique lo contrario:

(i) las evaporaciones se llevaron a cabo por evaporación rotatoria *in vacuo* y procedimientos de desarrollo se realizaron luego del retiro de sólidos residuales tales como agentes desecantes por filtración;

(ii) las operaciones se llevaron a cabo a temperatura de la sala, es decir en el rango 18-25°C y bajo una atmósfera de un gas inerte tal como argón o nitrógeno;

(iii) los rendimientos se dan para ilustración únicamente y no son necesariamente el máximo obtenible;

(iv) las estructuras de los productos finales de la Fórmula (I) se confirmaron por resonancia magnética nuclear (generalmente protónica) (NMR) con una fuerza de campo (para los protones) de 300MHz (empleando generalmente un Varian Gemini 2000) o 400 MHz (empleando generalmente un Bruker Avance DPX400), a menos que se especifique lo contrario, y técnicas de espectro de masas; los valores de desplazamiento químico de la resonancia magnética protónica se midieron en la escala delta y multiplicidades de pico se muestran como sigue: s, singlete; d, doblete; t, triplete; m, multiplete; br, amplio; q, cuartete, quin, quintete;

(v) Por lo general los intermedios no se caracterizaron completamente y la pureza se evaluó por cromatografía de capa fina (TLC), cromatografía de líquidos de alto rendimiento (HPLC), análisis infra-rojo (IR) o NMR;

(vi) Purificación por cromatografía se refiere generalmente a cromatografía en columna rápida, en sílice a menos que se especifique lo contrario. Por lo general se llevó a cabo cromatografía en columna usando cartuchos de sílice pre-empaquetados (de 4g hasta 400g) tales como Redisep™ (disponibles, por ejemplo, de Presearch Ltd, Hitchin, Herts, RU) o Biotage (Biotage UK Ltd, Hertford, Herts, UK), eluidos usando un sistema de bomba y colector de fracciones. La purificación mediante métodos de Extracción en Fase Sólida (SPE) se refiere generalmente al empleo de cartuchos de cromatografía empaquetados con materiales SPE tales como columnas SCX-2 ISOLUTE® (disponibles, por ejemplo, de International Sorbent Technology Ltd, Dryffryn Business Park, Hengoed, Mid Glamorgan, RU);

(vii) Los datos de espectros de masa (MS) se generaron en un sistema LCMS donde el componente HPLC incluía por lo general un equipo Agilent 1100 o Waters Alliance HT (2790 & 2795) y se corrieron en una columna Phemonenex Gemini C18 5µm, 50 x 2 mm (o similar) eluyendo con eluyente ácido (por ejemplo, usando una gradiente entre 0 - 95% agua/acetonitrilo con 5% de ácido fórmico al 1% en una mezcla 50:50 agua:acetonitrilo (v/v); o usando un distema disolvente equivalente con metanol en lugar de acetonitrilo), o un eluyente básico (por ejemplo, usando una gradiente entre 0 - 95% agua / acetonitrilo con 5% de una mezcla al 0.1% amoníaco 880 en acetonitrilo); y el componente MS incluía por lo general un espectrómetro Waters ZQ. Se generan los cromatogramas de Intensidad de Pico Base positivos y negativos para Electroaspersión (ESI), y el cromatograma de Absorción Total UV de 220-300nm, y se dan los valores para m/z; generalmente, sólo se relacionan los iones que indican la masa original y, a menos que se especifique lo contrario, el valor citado es $(M-H)^-$;

(viii) Reactores de microndas apropiados incluyen "Smith Creator", "CEM Explorer", "Biotage Initiator sixty" y "Biotage Initiator eight".

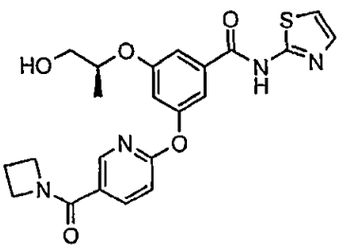
(ix) Los puntos de fusión se llevaron a cabo generalmente mediante Calorimetría Diferencial de Barrido (DSC); por lo general, los análisis se condujeron usando un equipo tal como un Mettler DSC822e o un Mettler DSC820. Las muestras de típicamente menos de 5 mg de material, contenidas en una cubeta de aluminio de 40 µL equipada con una tapa perforada, se calentaron en el rango de temperatura 25 °C a 325°C con una tasa de calentamiento constante de 10°C por minuto. Se empleó nitrógeno como gas de purga con un caudal de 100 mL por minuto. Se entenderá que los valores de temperatura de inicio y/o pico de la DSC pueden variar ligeramente de una máquina a otra, de un método a otro o de una muestra a otra y, en consecuencia, los valores citados no tienen que interpretarse como absolutas. Se observará que algunas muestras pueden ser solvatos y que este hecho puede afectar igualmente los puntos de fusión.

Abreviaturas

DCM	diclorometano;
DEAD	dietilazodicarboxilato;
DIAD	diisopropilazodicarboxilato;
DIPEA	*N*,*N*-Diisopropiletilamina;
DMA	dimetilacetamida;
DMSO	sulfóxido de dimetilo;
DMF	dimetilformamida;
EDAC	clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida;
HATU	hexafluorofosfato de *O*-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio;
HPLC	cromatografía de líquidos de alto rendimiento;
HPMC	hidroxipropilmetilcelulosa;
LCMS	cromatografía de líquidos/espectroscopía de masas;
NMP	*N*-metil-2-pirrolidona
NMR	espectroscopía de resonancia magnética nuclear;
RT	temperatura de la sala;
THF	tetrahidrofurano.
TFA	ácido trifluoroacético
$CDCl_3$	deuterocloroformo
$MgSO_4$	sulfato de magnesio
NaHMDS	hexametildisilazida de sodio

Todos los compuestos se derivaron usando un paquete de computación ACD NAME.

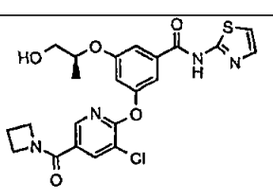
Ejemplo 1: 3-([5-(Azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-*N*-1,3-tiazol-2-ilbenzamida

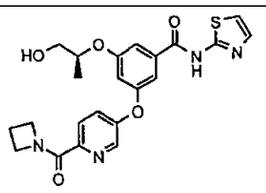
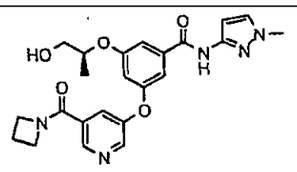
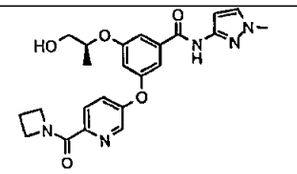


Una mezcla de 3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida (0.15 g, 0.33 mmol) en metanol (10 mL) y 1M ácido clorhídrico (10 mL) se agitó durante 90 minutos a temperatura de la sala. Los volátiles se retiraron *in vacuo* y el residuo se tomó a pH6 con solución de bicarbonato de sodio acuoso saturado, luego se extrajo en acetato de etilo (3 x 30 mL) y las capas orgánicas combinadas se lavaron con agua (30 mL), salmuera (30 mL), se secaron ($MgSO_4$), se filtraron y los disolventes se retiraron *in vacuo* a un residuo que se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en acetato de etilo para producir el compuesto deseado (65 mg).

^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.30 (s, 1H), 2.39 (quintete, 2H), 3.79 (m, 2H), 4.20-4.40 (brm, 4H), 4.58 (m, 1H), 6.98 (m, 2H), 7.27 (m, 1H), 7.35 (m, 1H), 7.39 (s, 1H), 7.41 (s, 1H), 8.11 (d, 1H), 8.41 (s, 1H), 11.50 (s, 1H). *m/z* 455 $(M+H)^+$

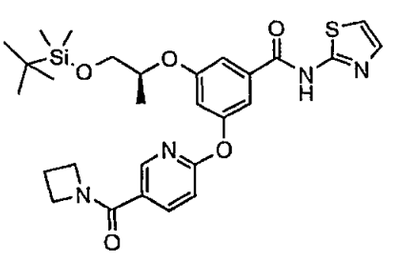
Los siguientes compuestos se sintetizaron en una forma análoga del silil éter apropiado.

Ejemplo	Estructura	m/z	NMR
1a		489, 491 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 3H), 2.25 (s, 1H), 2.43 (quintete, 2H), 3.77 (m, 2H), 4.20-4.40 (brm, 4H), 4.59 (m, 1H), 6.95 (d, 1H), 7.03 (s, 1H), 7.31 (d, 1H), 7.39 (s, 1H), 7.47 (s, 1H), 8.17 (s, 1H), 8.27 (s, 1H), 11.60 (brs, 1H).

1b		455 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.22 (d, 3H), 2.38 (m, 3H), 3.68 (m, 2H), 4.19 (t, 2H), 4.48 (m, 1H), 4.63 (t, 2H), 6.75 (m, 1H), 6.91 (d, 1H), 7.13 (s, 1H), 7.19 (m, 1H), 7.28 (m, 2H), 8.03 (d, 1H), 8.22 (s, 1H), 11.40 (brs, 1H).
1c		452 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.40 (quintete, 2H), 3.78 (m, 2H), 3.82 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.57 (sextete, 1H), 6.80 (d, 2H), 7.11 (s, 1H), 7.28 (m, 2H), 7.63 (s, 1H), 8.52 (s, 1H), 8.61 (s, 2H)
1d		452 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.26 (quintete, 2H), 2.48 (t, 1H), 3.67 (m, 2H), 3.69 (s, 3H), 4.18 (t, 2H), 4.45 (sextete, 1H), 4.63 (t, 2H), 6.70 (m, 2H), 7.05 (m, 1H), 7.20 (m, 2H), 7.28 (m, 1H), 8.02 (d, 1H), 8.21 (d, 1H), 8.73 (s, 1H)

La preparación de 3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida empleada en **Ejemplo 1** se describe a continuación:

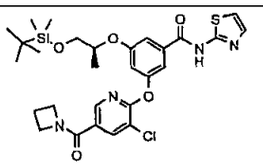
3-{[5-(Azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida



Carbonato de potasio (0.14 g, 0.98 mmol) se agregó a una mezcla de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-

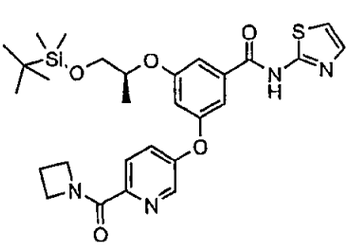
1,3-tiazol-2-ilbenzamida (200 mg, 0.49 mmol) y 5-(azetidin-1-ilcarbonil)-2-cloropiridina (96 mg, 0.49 mmol) en acetonitrilo (5.0 mL) y la mezcla agitada se calentó a 160°C en un 'Biotage initiator Microwave' durante 4 horas. La mezcla se dejó alcanzar la temperatura y presión de la sala y se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa de acetato de etilo se separó, se lavó con agua (5 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con una gradiente de 60-100% acetato de etilo en isohexano, para producir el compuesto deseado. (0.15 g). *m/z* 569 $(M+H)^+$

El precursor para **Ejemplo 1a** se preparó en una forma similar de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-1,3-tiazol-2-ilbenzamida empleando 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina:

Estructura	**m/z**	**NMR**
	603, 605 $(m+H)^+$	^{1}HNMR 8 ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.81 (s, 9H), 1.27 (d, 3H), 2.32 (quintete, 2H), 3.60-3.80 (m, 2H), 4.15-4.35 (brm, 4H), 4.45 (m, 1H), 6.83 (d, 1H), 6.95 (m, 1H), 7.19 (d, 1H), 7.25 (s, 1H), 7.30 (s, 1H), 8.08 (d, 1H), 8.17 (d, 1H), 11.95 (bra, 1H).

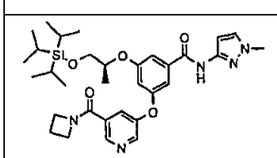
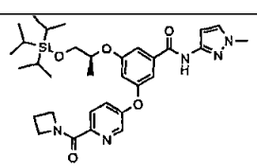
El precursor para **Ejemplo 1b** se preparó como se describe a continuación:

3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida



Carbonato de cesio (0.478 g, 1.47 mmol) se agregó a una mezcla de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-1,3-tiazol-2-ilbenzamida (200 mg, 0.49 mmol), bromotris(trifenilfosfina)cobre (46 mg, 0.049 mmol) y 2-(azetidin-1-ilcarbonil)-5-bromopiridina (130 mg, 5.39 mmol) en DMA (5.0 mL) y la mezcla agitada se calentó a 160°C en un 'Biotage initiator Microwave' durante 3 horas. La mezcla se dejó alcanzar la temperatura y presión de la sala y se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa de acetato de etilo se separó, se lavó con agua (5 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-100% acetato de etilo en isohexano, para producir el compuesto deseado. (47 mg).
^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.29 (d, 3H), 2.32 (quintete, 2H), 3.65-3.80 (m, 2H), 4.21 (t, 2H), 4.46 (m, 1H), 4.68 (t, 2H), 6.81 (s, 1H), 6.92 (m, 1H), 7.25 (m, 1H), 7.30-7.50 (m, 2H), 7.65 (m, 1H), 8.08 (d, 1H), 8.28 (s, 1H), 11.50 (brs, 1H). m/z 569 $(M+H)^+$

Los precursores para Ejemplos **1c-1d** se prepararon en una forma similar de 3-hidroxi-N-(1-metil-1*H*-pirazol-3-il)-5-[((1*S*)-1-metil-2-{[tris(1-metiletil)silil]oxi}etil)oxi]benzamida empleando la bromopiridina apropiada:

Estructura	**m/z**	**NMR**
	608 $(M+H)^+$	
	608 $(M+H)^+$	

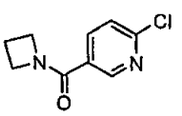
Bromotris(trifenilfosfina)cobre puede prepararse de acuerdo con Synthetic Communications, 31(18), 2865-2879 (2001). La preparación de bromotris(trifenilfosfina)cobre se describe a continuación.

Bromotris(trifenilfosfina)cobre

Bromuro de cobre (II) (111.7 g, 0.5 mol) se agregó en porciones a una solución agitada de trifenilfosfina (557.4 g, 2.13 mol) en metanol (1.85 L) a temperatura de la sala (se observó una exoterma a 32°C). La reacción se agitó durante 10 minutos, luego se calentó a 65°C y se enfrió de un día para otro. El sólido se recogió por filtración, se lavó con etanol (5 vol), éter dietílico (3 x 5 vol), se secó sobre material sinterizado bajo vacío durante 2 horas, luego en un horno de vacío a 30°C de un día para otro para proporcionar el producto como un sólido cristalino (460 g).

La preparación de 5-(azetidin-1-ilcarbonil)-2-cloropiridina empleada en la preparación de 3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[((1S)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida, un precursor de **Ejemplo 1**, se describe a continuación:

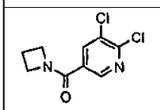
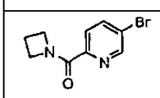
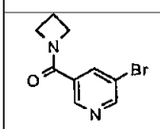
5-(Azetidin-1-ilcarbonil)-2-cloropiridina



DMF (2 gotas) se agregó a una solución de ácido 6-cloronicotínico (1.00 g, 6.35 mmol) y cloruro de oxalilo (0.67 mL, 7.62 mmol) en DCM (20 mL) y 2M cloruro de hidrógeno en éter (3.15 mL, 6.35 mmol). La mezcla se agitó a temperatura de la sala durante 4 horas y luego el DCM y el exceso de cloruro de oxalilo se evaporaron *in vacuo*. El cloruro de ácido residual se disolvió en DCM (10 mL) y se agregó a una mezcla de clorhidrato de azetidina (0.66 g, 6.99 mmol) y trietilamina (2.14 mL, 13.97 mmol) en DCM (10 mL), luego se agitó a temperatura de la sala durante 24 horas. El DCM se evaporó *in vacuo*, y el residuo se repartió en porciones entre acetato de etilo (100 mL) y 1M ácido cítrico (50 mL). La capa de acetato de etilo se lavó consecutivamente con bicarbonato de sodio acuoso saturado (50 mL) y salmuera (50 mL), se secó ($MgSO_4$), y el disolvente se retiró *in*

vacuo para producir un residuo, el cual se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (0.73 g). ^{1}H NMR δ ($CDCl_3$) 2.43 (quintete, 2H), 4.2-4.4 (brm, 4H), 7.42 (d, 1H), 7.97 (d, 1H), 8.63 (s, 1H). m/z 197 $(M+H)^+$

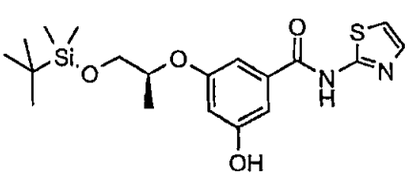
Las halopiridinas empleadas en la preparación de precursores para **Ejemplos 1a-1d** se prepararon en una forma similar del ácido nicotínico apropiado:

Estructura	m/z	NMR
		^{1}H NMR δ ($CDCl_3$): 2.43 (quintete, 2H), 4.21 - 4.44 (m, 4H), 8.11 (d, 1H), 8.53 (d, 1H)
	241,243 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.35(quintete, 2H), 4.25 (t, 2H), 4.70 (t, 2H), 7.93 (d, 1H), 8.03 (d, 1H), 8.63 (s, 1H).
	241,243 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.42 (quintete, 2H), 4.20 - 4.45 (m, 4H), 8.16 (t, 1H), 8.76 (t, 2H)

Los ácidos nicotínicos fueron o bien compuestos disponibles en el comercio o compuestos conocidos en la literatura. Referencia para 2-(azetidin-1-ilcarbonil)-5-bromopiridina (Heterocycles, 15(1) **1981**, 213-23).

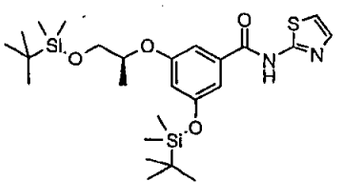
La preparación de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-1,3-tiazol-2-ilbenzamida empleada en la síntesis de **Ejemplo 1, 1a** y **1b** se describe a continuación:

3[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-1,3-tiazol-2-ilbenzamida



Una solución acuosa de monohidrato de hidróxido de litio (0.304 g, 7.25 mmol) se agregó a una solución de 3-{[(1,1-dimetiletil)(dimetil)silil] oxi}-5-[((1S)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida (1.552 g, 2.90 mmol) en THF (40 mL) y se agitó a temperatura de la sala de un día para otro. El THF se retiró *in vacuo* y la solución residual se ajustó a pH 7 mediante la adición de 1N ácido clorhídrico (7.25 mL). Se formó una goma, y la solución se filtró y la goma se disolvió en metanol. El filtrado se repartió en porciones con acetato de etilo (75 mL) y los orgánicos se lavaron con salmuera, se secaron ($MgSO_4$), se combinaron con la solución de metanol y se evaporaron a un residuo, el cual se cromatografió en sílice, eluyendo con 40% acetato de etilo en isohexano, para proporcionar el producto requerido (0.865 g)
^{1}H NMR δ ($CDCl_3$): -0.02 (d, 6H), 0.81 (s, 9H), 1.24 (d, 3H), 3.67 (m, 2H), 4.43 (sextete, 1H), 6.65 (t, 1H), 7.00 (d, 1H), 7.13 (t, 1H), 7.15 (t, 1H), 7.40 (d, 1H). m/z 409 $(M+H)^+$

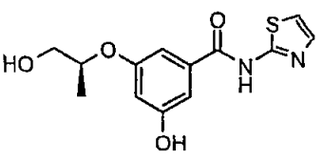
3-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-5-[((1*S*)-2-{(1,1- dimetiletil) (dimetil) silil]oxi}-1-metiletil)oxil-*N*-1,3-tiazol-2-ilbenzamida



Cloruro de *terc*-butildimetilsililo (1.66 g, 11.0 mmol) e imidazol (1.78 g, 26.0 mmol) se agregaron a una solución de 3-hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-1,3-tiazol-2-ilbenzamida (1.541 g, 5.24 mmol) en DMF (10 mL) y la reacción se agitó a temperatura de la sala bajo un tubo de secamiento de sílice de un día para otro. Se agregó agua (30 mL) y la solución se repartió en porciones con acetato de etilo (100 mL). La fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 15% acetato de etilo en isohexano, para proporcionar el producto requerido (1.525 g). ^{1}H NMR δ ($CDCl_3$): -0.17 (d, 6H), 0.00 (s, 6H), 0.65 (s, 9H), 0.76 (s, 9H), 1.08 (d, 3H),

3.50 (m, 2H), 4.25 (sextete, 1H), 6.43 (t, 1H), 6.77 (d, 1H), 6.83 (t, 1H), 6.96 (t, 1H), 7.06 (d, 1H). *m/z* 423 $(M-H)^-$

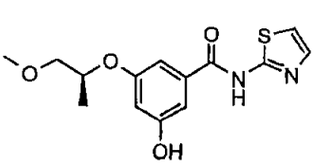
3-Hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-1,3-tiazol-2-ilbenzamida



Yodo(trimetil)silano (7.19 mL, 50.5 mmol) se agregó gota a gota a una solución de 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-1,3-tiazol-2-ilbenzamida (3.116 g, 10.1 mmol) en acetonitrilo (60 mL) bajo una atmósfera inerte y la reacción se agitó a temperatura de la sala de un día para otro. Se agregó metanol (5 mL) y la reacción se agitó durante 10 minutos más. Se agregaron una solución de tiosulfato de sodio saturado (5 mL) y una solución de carbonato de potasio saturado (5 mL) y la reacción se agitó durante 10 minutos más. Los disolventes orgánicos se retiraron *in vacuo* y la solución resultante repartida en porciones se extrajo con acetato de etilo (100 mL). La capa acuosa se ajustó a pH 5 con la adición de 1M ácido clorhídrico y se extrajo con acetato de etilo. Las capas orgánicas combinadas se lavaron con salmuera (20 mL), se secaron ($MgSO_4$), y se evaporaron a un residuo, el cual se cromatografió en sílice, eluyendo con acetato de etilo, para producir el compuesto deseado (1.541 g).

^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.52 (m, 2H), 4.50 (sextete, 1H), 6.55 (t, 1H), 7.04 (t, 1H), 7.18 (t, 1H), 7.27 (d, 1H), 7.55 (d, 1H), 12.47 (s, 1H). m/z 295 $(M+H)^+$

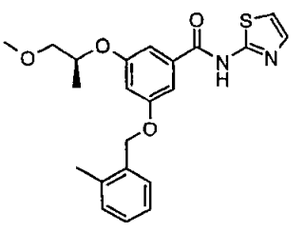
3-Hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-1,3-tiazol-2-ilbenzamida



Una solución de 3-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-5-{[(2-metilfenil) metil]oxi}-*N*-1,3-tiazol-2-ilbenzamida (6.9 g) y tioanisol (10 mL) en ácido

trifluoroacético (65 mL) se agitó a temperatura ambiente durante 16 horas. Se retiró el ácido trifluoroacético *in vacuo* y el aceite residual se repartió en porciones entre acetato de etilo (75 mL) y solución de bicarbonato de sodio acuoso (200 mL). La capa acuosa se separó, se extrajo con acetato de etilo (2 x 75 mL), y los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y se evaporaron a un residuo, el cual se cromatografió en sílice con 50% acetato de etilo en isohexano como eluyente para producir el compuesto deseado (4.6 g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.5-4.6 (m, 1H), 6.65 (s, 1H), 6.95 (d, 1H), 7.05 (s, 1H), 7.1 (s, 1H), 7.25 (d, 1H). m/z 309 $(M+H)^+$

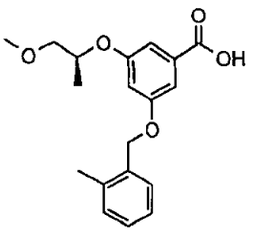
3-{[(1*S*)-2-Metoxi-(1-metiletil)oxi}-5-{[(2-metilfenil)metil] oxi}-N-1,3-tiazol-2-ilbenzamida



A una solución de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[(2-metilfenil)metil]oxi}benzoico (9.55 g) en DCM (140 mL) se agregó cloruro de oxalilo (2.83 mL), seguido por DMF (1 gota), y la mezcla se agitó a temperatura ambiente durante 16 horas. El DCM y el exceso de cloruro de oxalilo se retiraron *in vacuo*, el aceite residual se disolvió en DCM (25 mL) y se agregó a una solución de 2-aminotiazol (2.84g) y trietilamina (7.88 mL) en DCM (75 mL) a 0-5°C, y la mezcla se agitó a temperatura ambiente durante 4 horas. El DCM y el exceso de trietilamina se retiraron *in vacuo*, el aceite residual se repartió en porciones entre acetato de etilo (100 mL) y 1M ácido clorhídrico (100 mL). La capa de acetato de etilo se separó, se lavó consecutivamente con 1M ácido clorhídrico, solución de bicarbonato de sodio acuoso, y salmuera, se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió sobre alúmina con acetato de etilo como eluyente para producir el compuesto deseado (11.0 g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d,

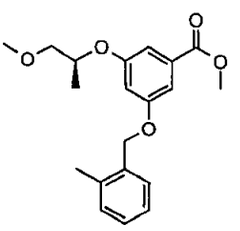
3H), 2.35 (s,3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.55-4.6 (m, 1H), 5.0 (s,2H), 6.8 (s, 1H), 6.95 (d, 1H), 7.15 (s, 1H), 7.25 (m, 5H), 7.4 (d, 1H). *m/z* 413 $(M+H)^+$

Ácido 3-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-5-{[(2-metilfenil)metil]oxi} benzoico



Una solución de metil 3-[{(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[(2-metilfenil)metil]oxi}benzoato (10.65g) en THF (200 mL) y metanol (50 mL) se agregó a una solución de monohidrato de hidróxido de litio (6.0g) en agua (100 mL). La mezcla se agitó a temperatura ambiente durante 16 horas y el THF y el metanol se retiraron *in vacuo*. La capa acuosa se acidificó a pH1 con ácido clorhídrico, y se extrajo con acetato de etilo (3 x 50 mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y se evaporaron para producir el compuesto deseado (9.55 g). *m/z* 329 $(M-H)^-$

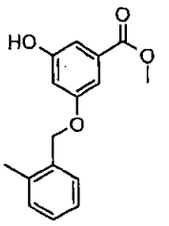
Metil 3-[{(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[(2-metilfenil) metil]oxi} benzoato



Una suspensión agitada de metil 3-hidroxi-5-{[(2-metilfenil) metil]oxi}benzoato (15.3 g) y trifenil fosfina soportada en polímero (39.2 g) en DCM seco (900 mL) se enfrió en un baño helado y se agregó gota a gota diisopropil azodicarboxilato (11.88 mL). La mezcla de reacción se agitó a 0-5°C durante 30 minutos y se agregó gota a gota(*R*)-1-metoxi-propan-2-ol.

La mezcla de reacción se agitó a temperatura ambiente durante 16 horas, se filtró a través de tierra de diatomeas y el DCM se evaporó a un residuo, el cual se cromatografió en sílice con 10% acetato de etilo en isohexano como eluyente para producir el compuesto deseado (10.7 g). ^{1}HNMR δ ($CDCl_3$): 1.3 (d, 3H), 2.4 (s, 3H), 3.4 (s, 3H), 3.5- 3.6 (m, 2H), 3.9 (s, 3H), 4.55-4.6 (m, 1H), 5.0 (s, 2H), 6.8 (s, 1H), 7.25 (m, 5H), 7.4 (d, 1H)

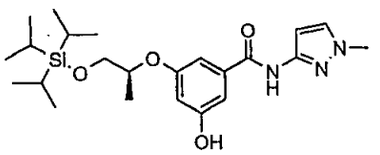
Metil 3-hidroxi-5-{[(2-metilfenil)metil]oxi}benzoato



A una solución de metil 3,5-dihidroxibenzoato (50 g, 0.30 mol) en DMF (500 mL) a 0°C se agregó hidruro de sodio (10.8 g, 0.27 mol) en porciones, manteniendo la temperatura de reacción por debajo de 10°C. La reacción se dejó calentar a 15°C, y se agitó durante 20 minutos. La mezcla se enfrió a 0°C y se agregó durante 30 minutos una solución de bromuro de 2-metilbencilo (36 mL, 0.27 mol) en DMF (50 mL). La reacción se calentó a temperatura ambiente y se concentró *in vacuo*, el aceite residual se repartió en porciones entre acetato de etilo (500 mL) y agua (250 mL), la capa de acetato de etilo se separó, se lavó consecutivamente con agua y salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice eluyendo con una gradiente de 0-100% acetato de etilo en isohexano para producir el compuesto deseado (21.9 g). ^{1}H NMR δ ($CDCl_3$) 2.39 (s, 3H), 3.90 (s, 3H), 5.02 (s, 2H), 5.61 (s, 1H), 6.69 (t, 1H), 7.15-7.42 (m, 6H).

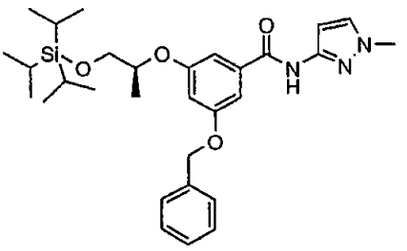
La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[((1*S*)-1-metil-2-{[tris(1-metiletil)silil]oxi}etil)oxi]benzamida empleada en la síntesis de **Ejemplo 1c-1d** se describe a continuación:

3-Hidroxi-*N*-(1-metil-1H-pirazol-3-il)-5-[((1*S*)-metil-2-{[tris(1-metiletil)silil]oxi}etil)oxi]benzamida



10% Paladio sobre carbón se agregó a 3-(benciloxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-{(1*S*)-1-metil-2-[(triisopropilsilil)oxi]etoxi}benzamida (21.7 g, 40.4 mmol) en THF seco (480 mL) bajo argón. La mezcla de reacción se desgasificó y se puso bajo un balón de hidrógeno y se agitó durante 16 horas. La atmósfera se reemplazó con argón y la mezcla se filtró a través de tierra de diatomeas, seguidamente el filtrado se evaporó y se secó bajo alto vacío durante 1 hora para producir el compuesto del título (18.2 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.3 (d, 3H), 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 4.5 (m, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.20 (s, 1H), 7.3 (s, 1H), 8.7 (s, 1H). *m/z* 448 $(M+H)^+$, 446 $(M-H)^-$

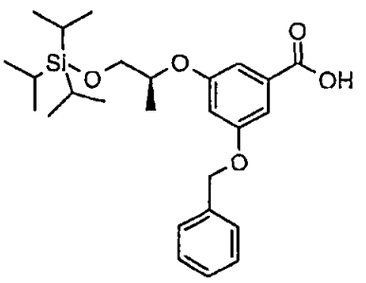
3-(Benciloxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-{(1*S*)-1-metil-2-[(triisopropilsil)oxi]etoxi}benzamida



HATU (23.5 g, 61.8 mmol) se agregó a ácido 3-(benciloxi)-5-{(1*S*)-1-metil-2-[(triisopropilsilil)oxi]etoxi}benzoico (23.6 g, 51.5 mmol), seguido por la adición de DMF (140 mL), y se enfrió a 0°C. Se agregó 3-amino-1-metilpirazol (6.00 g. 61.8 mmol) seguido por DIPEA (21.3 mL) y la reacción se agitó bajo argón a 0°C durante 3 horas. El disolvente se evaporó y el residuo se disolvió en acetato de etilo (500 mL) y se lavó con solución de ácido cítrico (200 mL), solución de bicarbonato de sodio (150 mL), y solución de salmuera saturada (2 x 150mL). La capa orgánica se separó y se secó ($MgSO_4$), se filtró y se evaporó. La purificación por

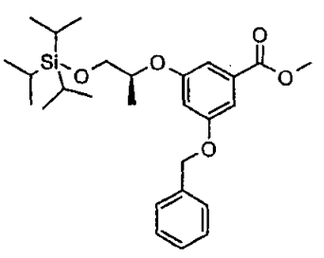
cromatografía en columna, eluyendo con 1:4 a 1:1 acetato de etilo:hexanos, produjo el compuesto del título como un aceite incoloro (21.7g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.3 (d, 3H), 3.7 (m, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 4.5 (m, 1H), 5.1 (s, 2H), 6.7 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.1 (s, 1H), 7.3 (s, 1H), 7.35 -7.5 (m, 5H), 8.5 (s, 1H). *m/z* 538 $(M+H)^+$

Ácido 3-(benciloxi)-5-{(1*S*)-1-metil-2-[(triisopropilsil)oxi]etoxi}benzoico



Monohidrato de hidróxido de litio (12.14 g, 0.289 mol) en agua (100 mL) se agregó a una solución de metil 3-(benciloxi)-5-{(1*S*)-1-metil-2-[(triisopropilsilil)oxi]etoxi}benzoato (62 g, 0.131 mol) en THF (300 mL) y calentó a 43°C. La reacción se agitó durante 16 horas, se retiró el THF *in vacuo* y la mezcla resultante se acidificó a pH 5 con 10% p/v ácido cítrico. Esto se extrajo con acetato de etilo (2 x 300 mL) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se evaporaron para producir el compuesto del título (60.2 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.35 (d, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 4.5 (m, 1H), 5.1 (s, 2H), 6.8 (s, 1H), 7.3 -7.5 (m, 7H). *m/z* 457 $(M-H)^-$

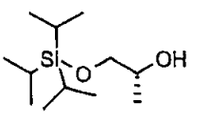
Metil 3-(benciloxi)-5-{(1*S*)-1-metil-2-[(triisopropilsilil)oxi]etoxi} benzoato



(2*R*)-1-[(Triisopropilsilil)oxi]propan-2-ol (56.1 g, 242 mmol) se agregó a una solución de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (50 g, 194 mmol) y trifenilfosfina (63.5 g, 242 mmol) en THF seco (500 mL), a 0°C,

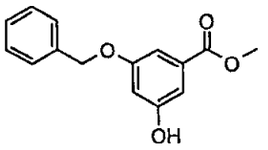
seguido por la adición de DIAD (47.6 mL, 242 mmol) durante 45 minutos bajo una atmósfera de argón. La reacción se agitó a 0°C durante 1 hora y se dejó calentar a temperatura de la sala durante hora, luego se agitó a temperatura de la sala durante 1 hora. El THF se evaporó y se agregó una mezcla de acetato de etilo (80 mL) y hexano (120 mL). Esta mezcla se agitó durante 2 horas y se filtró. El precipitado se lavó con una mezcla de acetato de etilo (20 mL) y hexano (180 mL) y el filtrado se evaporó. El residuo se purificó por cromatografía en columna, eluyendo con 1:20 a 1:10 acetato de etilo:hexanos, para producir el compuesto del título (65.5 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.35 (d, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 3.9 (s, 3H), 4.5 (m, 1H), 5.05 (s, 2H), 6.75 (s, 1H), 7.2 (s, 1H). 7.3 -7.5 (m, 6H). *m/z* 471 $(M-H)^-$

(2*R*)-1-[(Triisopropilsilil)oxi]propan-2-ol



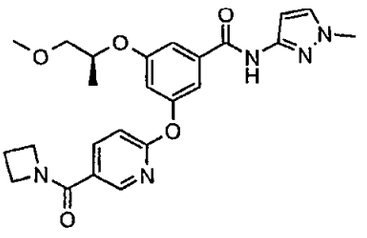
Cloruro de triisopropilsililo (83.8 mL, 390 mmol) se agregó lentamente durante 15 minutos a una solución de (2*R*)-propano-1,2-diol (29.7 g, 390 mmol) en DMF a 0°C (100 mL) manteniendo la temperatura interna por debajo de 15°C. Esto fue seguido por la adición de imidazol (66.4 g, 975 mmol) y la mezcla de reacción se dejó calentar a temperatura de la sala y se agitó bajo argón durante 20 horas. La reacción se extinguió con 1M ácido clorhídrico/éter dietílico (300 mL/800 mL). La capa orgánica se separó y se lavó con 1M ácido clorhídrico seguido por solución de salmuera saturada. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó. La purificación mediante destilación a 10mmHg, 90-104°C, produjo el compuesto del título como un aceite incoloro (69.5 g). ^{1}H NMR δ ($CDCl_3$): 1.05 (s, 18H), 1.05-1.1 (m, 3H), 1.05 (d, 3H), 2.55 (s, 1H), 3.45 (dd, 1H), 3.7 (dd, 1H), 3.85 (m, 1H).

Metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato



A una solución agitada de metil 3,5-dihidroxibenzoato (5.95 mol) en DMF (6 L) se agregó carbonato de potasio (9 mol), y la suspensión se agitó a temperatura ambiente bajo argón. A esto se agregó bromuro de bencilo (8.42 mol) lentamente durante 1 hora, con una ligera exoterma, y la mezcla de reacción se agitó de un día para otro a temperatura ambiente. La reacción se extinguió cuidadosamente con solución de cloruro de amonio (5 L) seguido por agua (35 L). La suspensión acuosa se extrajo con DCM (1 x 3 L y 2 x 5 L). Los extractos combinados se lavaron con agua (10 L) y se secaron de un día para otro ($MgSO_4$). La solución se evaporó *in vacuo*; y el producto crudo se cromatografió en 3 lotes (columna rápida, 3 x 2 kg sílice, eluyendo con una gradiente compuesta de hexano que contenía 10% DCM, a DCM puro, a DCM que contenía 50% acetato de etilo) para eliminar el material de partida. El eluyente crudo se cromatografió posteriormente lotes de 175 g (Amicon HPLC, 5 kg sílice de fase normal, eluyendo con isohexano que contenía 20% v/v de acetato de etilo) para producir el compuesto deseado (21% de rendimiento). ^{1}H NMR δ (d_6-DMSO): 3.8 (s, 3H), 5.1 (s, 2H), 6.65 (m, 1H), 7.0 (m, 1H), 7.05 (m, 1H), 7.3-7.5 (m, 5H), 9.85 (br s, 1H).

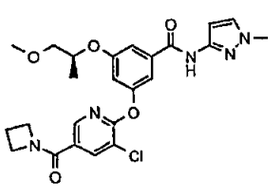
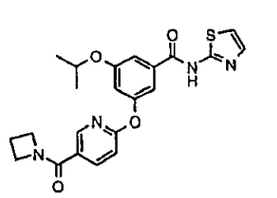
Ejemplo 2: 3-{[5-(Azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida

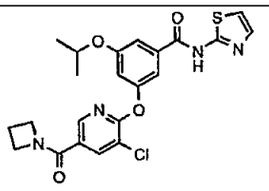
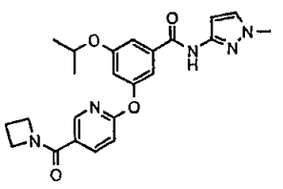
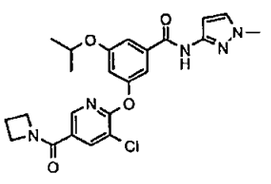
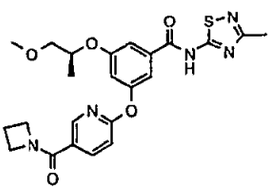
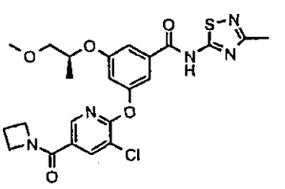


Carbonato de potasio (0.181 g, 1.31 mmol) se agregó a una mezcla de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-

il)benzamida (0.2 g, 0.66 mmol) y 5-(azetidin-1-ilcarbonil)-2-cloropiridina (129 mg, 0.66 mmol) en acetonitrilo (5.0 mL), y la mezcla agitada se calentó a 160°C en un 'Biotage initiator Microwave' durante 6 horas. La mezcla se dejó alcanzar la temperatura y presión de la sala y se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa de acetato de etilo se separó, se lavó con agua (5 x 50 mL) salmuera (50 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-5% metanol en acetato de etilo, para producir el compuesto deseado (202 mg). ^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.38 (quintete, 2H), 3.40 (s, 3H), 3.61 - 3.47 (m, 2H), 3.74 (s, 3H), 4.42 - 4.18 (m, 4H), 4.58 (sextete, 1H), 6.80 (d, 1H), 6.91 (t, 1H), 6.97 (d, 1H), 7.21 (t, 1H), 7.26 (d, 1H), 7.33 (t, 1H), 8.09 - 8.05 (m, 1H), 8.42 (d, 1H), 8.92 (s, 1H); *m/z* 466 $(M+H)^+$

En una manera similar, se prepararon los **Ejemplos 2a-2g** empleando el fenol y la halopiridina apropiados:

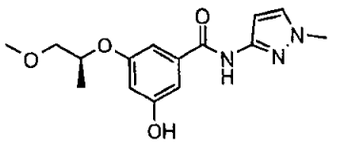
Ejemplo	Estructura	m/z	NMR
2a		500 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 3H), 2.36 (quintete, 2H), 3.38 (s, 3H), 3.59 - 3.45 (m, 2H), 3.67 (s, 3H), 4.39 - 4.15 (m, 4H), 4.55 (sextete, 1H), 6.79 (d, 1H), 6.92 (t, 1H), 7.20 (t, 1H), 7.25 (d, 1H), 7.35 (t, 1H), 8.14 (d, 1H), 8.20 (d, 1H), 9.42 (s, 1H)
2b		439 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.36 (d, 6H), 2.39 (m, 2H), 4.42 - 4.19 (m, 4H), 4.58 (septete, 1H), 6.90 (d, 1H), 6.93 (t, 1H), 6.98 (d, 1H), 7.22 (d, 1H), 7.34 (t, 1H), 7.40 (m, 1H), 8.08 (m, 1H), 8.41 (d, 1H), 12.21 (s, 1H)
2c		473 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.39 (quintete, 2H), 4.39 - 4.20 (m, 4H), 4.59 (septete, 1H), 6.92 (d, 1H), 6.96 (t, 1H), 7.23 (d, 1H), 7.36 (t, 1H), 7.44 (t,

			1H), 8.16 (d, 1H), 8.23 (d, 1H), 12.37 (s, 1H)
2d		436 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.32 (d, 6H), 2.34 (quintete, 2H), 3.71 (s, 3H), 4.37 - 4.17 (m, 4H), 4.54 (septete, 1H), 6.77 (d, 1H), 6.82 (t, 1H), 6.94 (d, 1H), 7.15 (t, 1H), 7.23 (d, 1H), 7.25 (m, 1H), 8.04 (m, 1H), 8.38 (d, 1H), 8.85 (s, 1H)
2e		470 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.40 (quintete, 2H), 3.78 (s, 3H), 4.41 - 4.20 (m, 4H), 4.61 (septete, 1H), 6.81 (d, 1H), 6.89 (t, 1H), 7.20 (t, 1H), 7.29 (m, 1H), 7.32 (t, 1H), 8.17 (d, 1H), 8.25 (d, 1H), 8.72 (s, 1H)
2f		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.39 (quintete, 2H), 2.47 (s, 3H), 3.41 (s, 3H), 3.63 - 3.49 (m, 2H), 4.43 - 4.20 (m, 4H), 4.61 (sextete, 1H), 7.00 (m, 2H), 7.37 (t, 1H), 7.44 (t, 1H), 8.40 (d, 1H), 11.08 (s, 1H)
2g		518 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.40 (quintete, 2H), 2.44 (s, 3H), 3.41 (s, 3H), 3.64 - 3.49 (m, 2H), 4.45 - 4.20 (m, 4H), 4.61 (sextete, 1H), 7.04 (t, 1H), 7.40 (t, 1H), 7.42 (s, 1H), 8.17 (d, 1H), 8.21 (d, 1H), 11.32 (s, 1H)

La preparación de las halopiridinas se describe en **Ejemplo 1.**

La preparación de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida empleada en la síntesis de **Ejemplos 2** y **2a** se describe a continuación:

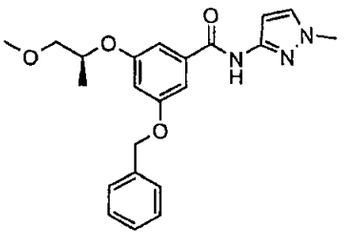
3-Hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



A una solución de 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1H-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (7.07 g) en THF (50 mL) y metanol (50 mL) se agregó 10% paladio sobre carbón (727 mg) como una suspensión (***"a slurry"***) en THF (1 mL) y metanol (1 mL). La mezcla se puso bajo vacío y se agitó bajo una atmósfera de hidrógeno durante 70 horas. La mezcla se filtró a través de tierra de diatomeas, y la tierra de diatomeasse lavó con metanol (2 x 100 mL), seguido por evaporación *in vacuo*. Los residuos se disolvieron en acetato de etilo (10 mL), se trataron con isohexano (40 mL), se extrajo el sólido completamente por filtración y se lavó con isohexano (50 mL) para producir el compuesto deseado (5.17 g), el cual se utilizó sin purificación posterior.

^{1}H NMR δ (d_6-DMSO): 1.22 (d, 3H), 3.28 (s, 3H, oscurecido por agua), 3.38-3.53 (m, 2H), 3.76 (s, 3H), 4.65 (m, 1H), 6.44 (m, 1H), 6.54 (m, 1H), 6.93 (s, 1H), 7.04 (s, 1H), 7.57 (m, 1H), 9.63 (br s, 1H), 10.60 (s, 1H). *m/z* 306 $(M+H)^+$, 304 $(M-H)^-$

3-[(1*S*)-2-Metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida

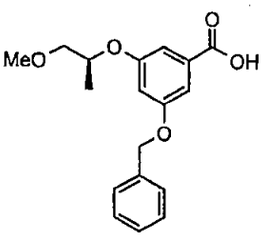


Una solución de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil] oxi}benzoico (8.73 g) en DCM (150 mL) se enfrió a 0°C. Cloruro de oxalilo (4.81 mL) y DMF (0.15 mL) se agregaron lentamente agitando al mismo tiempo. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 16 horas, luego de lo cual los orgánicos se retiraron *in vacuo*, y los residuos se destilaron bajo una temperatura fija (***"were azeotroped"***)

con tolueno (75 mL). El material crudo se disolvió en DCM (75 mL) y se agregó lentamente a una suspensión agitada de 3-amino-1-metilpirazol (3.35 g) y DIPEA (14.4 mL) en DCM (75 mL). La mezcla se agitó a temperatura ambiente durante 18 horas, antes de evaporar los orgánicos *in vacuo* y disolver el residuo en acetato de etilo (150 mL). Los orgánicos se lavaron con 1M ácido clorhídrico acuoso (100 mL) y salmuera (50 mL), y se secaron ($MgSO_4$), antes de la evaporación *in vacuo* para producir el material crudo. Éste se cromatografió en una columna SiO_2 200g Biotage Flash 75 (eluyendo con 30 a 90% acetato de etilo en isohexano), y se evaporó *in vacuo* para producir el compuesto deseado (7.07 g).

^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 3.28 (s, 3H, oscurecido por agua), 3.40-3.52 (m, 2H), 3.77 (s, 3H), 4.70 (m, 1H), 5.03 (s, 2H), 6.56 (m, 1H), 6.71 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H)$_3$ 7.32-7.47 (br m, 5H), 7.58 (m, 1H), 10.73 (s, 1H). *m/z* 396 $(M+H)^+$.

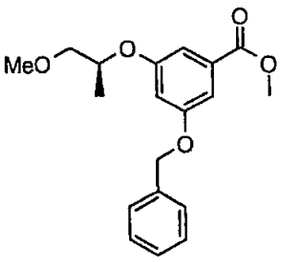
Ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico



Una solución de metil 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoato (77.4 mmol) en una mezcla de THF (232 mL) y metanol (232 mL) se trató con una solución de 2M hidróxido de sodio (232 mmol), y la mezcla de reacción se agitó durante 4 horas a temperatura ambiente. La solución resultante se diluyó con agua (250 mL) y la mayor parte del disolvente orgánico se retiró *in vacuo*. La suspensión resultante se lavó con éter dietílico (3 x 200 mL) y los lavados orgánicos se desecharon. La solución acuosa resultante se acidificó a pH4 con solución 2M ácido clorhídrico y se extrajo con acetato de etilo (2 x 200 mL). Los extractos se combinaron, se lavaron con salmuera, se secaron ($MgSO_4$), y se evaporaron para producir el compuesto deseado (99% de rendimiento).

^{1}H NMR δ (d_6-DMSO): 1.20 (d, 3H), 3.46 (m, 2H), 4.64 (m, 1H), 5.15 (s, 2H), 6.83 (app t, 1H), 7.06 (s, 1H), 7.13 (s, 1H), 7.30-7.49 (m, 5H), 12.67 (br s, 1H)

Metil 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoato



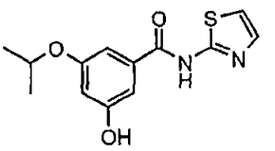
A una solución de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (77.4 mmol) en THF se agregó trifenilfosfina soportada en polímero (51.7g de carga 3 mmol/g, 155 mmol) y (*R*)-(-)-1-metoxi-2-propanol (102 mmol). La solución agitada se cubrió con argón y se enfrió en un baño helado. Una solución de DIAD (116 mmol) se agregó gota a gota mediante una jeringa durante 10 minutos. La solución se agitó durante 20 minutos y el filtró, lavando el residuo con THF (500 mL). El filtrado y los lavados se combinaron, y se evaporaron para producir el compuesto deseado, el cual se utilizó sin purificación posterior. ^{1}H NMR δ (d_6-DMSO): 3.26 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.63 (m, 1H), 5.14 (s, 2H), 6.85 (s, 1H), 7.05 (s, 1H), 7.11 (s, 1H), 7.30-7.47 (m, 5H).

El espectro ^{1}H NMR contenía también señales consistentes con una pequeña cantidad de bis(1-metiletil)hidrazin-1,2-dicarboxilato.

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describe en **Ejemplo 1c**.

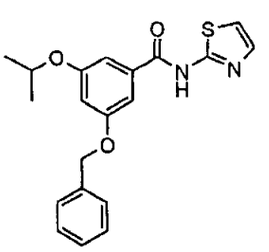
La preparación de 3-hidroxi-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida empleada en la preparación de **Ejemplos 2b** y **2c** se describe a continuación:

3-Hidroxi-5-[(1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida



3-[(1-Metiletil)oxi]-5-[(fenilmetil)oxi]-*N*-1,3-tiazol-2-ilbenzamida (11.2 g) se disolvió en ácido trifluoroacético (60 mL) y se trató con tioanisol (17.8 mL). La mezcla se dejó agitando a temperatura ambiente durante 18 horas antes de retirar el ácido trifluoroacético *in vacuo*. Los residuos se trataron con isohexano (100 mL) y el sólido se extrajo completamente por filtración, antes de lavar con más isohexano (2 x 20 mL). El sólido se disolvió en acetato de etilo (200 mL) y se lavó con solución de bicarbonato de sodio saturado acuoso (100 mL). Los orgánicos se lavaron con agua (100 mL) y salmuera (100 mL), y se secaron ($MgSO_4$) antes de la evaporación *in vacuo* para producir un sólido, el cual se lavó con isohexano (200 mL) y se secó *in vacuo* para producir el compuesto deseado (7.18 g). ^{1}H NMR δ (d_6-DMSO): 1.27 (d, 6H), 4.55 (m, 1H), 6.49 (m, 1H), 7.02 (s, 1H), 7.14 (s, 1H), 7.25 (d, 1H), 7.54 (d, 1H), 9.73 (s, 1H), 12.44 (s, 1H). *m/z* 279 $(M+H)^+$, 277 $(M-H)^-$

3-[(1-Metiletil)oxi]-5-[(fenilmetil)oxi]-*N*-1,3-tiazol-2-ilbenzamida



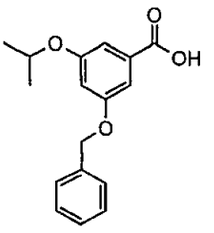
A una solución de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico (20 g) en DCM (400 mL), enfriado a 0°C se agregó lentamente cloruro de oxalilo (12.2 mL) y DMF (0.4 mL), agitando simultáneamente. La mezcla se dejó calentar a temperatura ambiente y se agitó durante 16 horas más, luego de lo cual los orgánicos se retiraron *in vacuo*, y los residuos se destilaron bajo una temperatura fija (***"were azeotroped"***) con tolueno (100 mL). El material crudo se disolvió en DCM (200 mL) y se agregó

lentamente a una suspensión agitada de 2-aminotiazol (10.5 g) y diisopropiletilamina (24.3 mL), en DCM (200 mL). La mezcla se agitó a temperatura ambiente durante 70 horas, antes de retirar los orgánicos *in vacuo*. Los residuos se disolvieron en acetato de etilo (300 mL) y se lavaron con 1M ácido clorhídrico acuoso (300 mL). La capa acuosa se extrajo con más acetato de etilo (300 mL), y los orgánicos combinados se lavaron con salmuera (75 mL), y se secaron ($MgSO_4$), antes de la evaporación *in vacuo* para producir el compuesto deseado (28 g), el cual se utilizó sin purificación posterior.

^{1}H NMR δ (d_6-DMSO): 1.27 (d, 6H), 4.70 (m, 1H), 5.15 (s, 2H), 6.77 (m, 1H), 7.27 (m, 2H), 7.33-7.47 (brm, 6H), 7.55 (d, 1H). *m/z* 369 $(M+H)^+$, 367 $(M-H)^-$;

El espectro ^{1}H NMR contenía también señales consistentes con una pequeña cantidad de acetato de etilo.

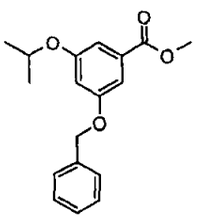
Ácido 3-[(1-metiletil)oxil-5-[(fenilmetil)oxi]benzoico



A una solución de metil 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi] benzoato (37 g) en una mezcla 1:1 de THF:metanol (300 mL) se agregó 4M solución de hidróxido de sodio (150 mL). La mezcla se hizo refluir durante 45 minutos, luego de lo cual los orgánicos se retiraron *in vacuo*. La capa acuosa se acidificó a pH4 con ácido clorhídrico (2M), y se extrajo con acetato de etilo. Los orgánicos se combinaron, se lavaron con agua y salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para producir el compuesto deseado (33.5 g), el cual se utilizó sin purificación posterior.

^{1}H NMR δ (d_6-DMSO): 1.26 (d, 6H), 4.59-4.69 (m, 1H), 5.15 (s, 2H), 6.80 (app t, 1H), 7.04 (m, 1H), 7.12 (m, 1H), 7.33 (app t, 1H), 7.40 (t, 2H), 7.46 (d, 2H), 12.95 (s, 1H).

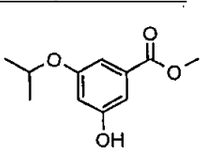
Metil 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoato



A una solución de metil 3-hidroxi-5-[(1-metiletil)oxi]benzoato (25 g) en DMF (250 mL) se agregó carbonato de potasio anhidro (297 mmol), y bromuro de bencilo (143 mmol). La mezcla se agitó a 60°C durante 5 horas, luego se enfrió a temperatura de la sala. El disolvente se retiró *in vacuo* y el residuo se repartió en porciones entre acetato de etilo y agua. Los orgánicos se combinaron y se lavaron con más agua, salmuera, se secaron ($MgSO_4$) y se concentraron *in vacuo* para producir el compuesto deseado (37 g), el cual se utilizó sin purificación posterior.

^{1}H NMR δ (d_6-DMSO): 1.26 (d, 6H), 3.84 (s, 3H), 4.61-4.70 (m, 1H), 5.12 (s, 2H), 6.84 (t, 1H), 7.05 (app t, 1H), 7.12-7.15 (m, 1H), 7.31-7.37 (m, 1H), 7.40 (t, 2H), 7.46 (d, 2H)

Metil 3-hidroxi-5-[(1-metiletil)oxi]benzoato

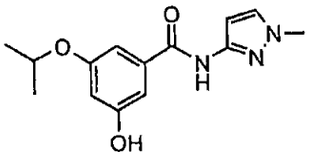


A una solución agitada de metil 3,5-dihidroxibenzoato (0.1 mol) en DMF (180 mL) se agregó carbonato de potasio en polvo (0.2 mol) y 2-yodopropano (0.1 mol), y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se vertió en agua (1.000 mL) y la mezcla se extrajo con éter. Los extractos se combinaron y se lavaron consecutivamente con agua (dos veces) y salmuera; la solución se secó ($MgSO_4$), se filtró y se evaporó *in vacuo* para producir el producto crudo como un aceite amarillo pálido (12.6 g). Éste se trató con tolueno (40 mL) y se dejó reposar de un día para otro. El material insoluble (fenol de partida) se retiró por filtración, y el filtrado se evaporó *in vacuo*. El aceite

resultante se cromatografió (cartuchos de sílice 2 x 90 g Biotage), eluyendo con hexano que contenía acetato de etilo (10% aumentando a 15% v/v). El compuesto del título se obtuvo como un aceite (25% de rendimiento), el cual fue idéntico mediante cromatografía de capa fina a una muestra preparada por un procedimiento similar. ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 6H), 3.8 (s, 3H), 4.5 - 4.6 (hept, 1H), 6.55 (m, 1H), 7.85 (m, 1H), 7.95 (m, 1H), 9.8 (s, 1H)

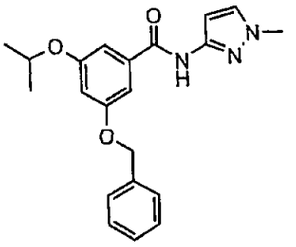
La preparación de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida empleada en **Ejemplo 2d** y **2e** se describe a continuación:

3-Hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



3-[(1-Metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil) oxi]benzamida (51g; 0.14mol) se disolvió en metanol (500 mL) y THF (500 mL) y el matraz se vació y se purgó con argón (3 veces). 10% Paladio sobre carbón (5.1 g) se agregó y el matraz se volvió a vaciar y, finalmente, se purgó con gas hidrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 20 horas. La mezcla de reacción se vació y se purgó con nitrógeno (3 veces). El catalizador se extrajo completamente por filtración a través de celita, y el filtrado se concentró *in vacuo*. Acetato de etilo se agregó y se filtró para producir el compuesto deseado (30.5 g). Una segunda recolección de material se obtuvo del mismo modo (4.0 g).
^{1}H NMR δ (d_6-DMSO): 1.30 (d, 6H), 3.78 (s, 3H), 4.68 (septete, 1H), 6.47 (m, 1H), 6.60 (s, 1H), 6.94 (s, 1H), 7.05 (s, 1H), 7.60 (s, 1H), 10.63 (s, 1H).
m/z 276 $(M+H)^+$

3-[(1-Metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi] benzamida

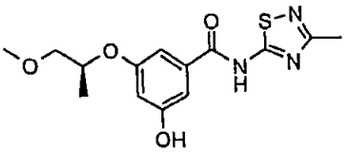


DMF (2 gotas) se agregó a una solución de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico (40.0 g, 0.14 mol) y cloruro de oxalilo (14.6 mL, 0.17 mol) en DCM (700 mL). La mezcla se agitó a temperatura ambiente durante 4 horas y el DCM y el exceso de cloruro de oxalilo se evaporaron *in vacuo*. El cloruro ácido residual se disolvió en DCM (300 mL) y se agregó gota a gota a 1-metil-3-aminopirazol (14.25 g, 0.147 mol) y trietilamina (41 mL, 0.29 mol) en DCM (300 mL), a 0°C. Se agitó a temperatura ambiente durante 24 horas. El DCM se evaporó *in vacuo*, y el residuo se repartió en porciones entre acetato de etilo (400 mL) y 1N ácido clorhídrico (200 mL). La capa de acetato de etilo se lavó consecutivamente con bicarbonato de sodio acuoso saturado (200 mL) y salmuera (100 mL), se secó ($MgSO_4$) y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 50% acetato de etilo en isohexano, para producir el compuesto deseado (51 g). ^{1}H NMR δ ($CDCl_3$): 1.30 (d, 6H), 3.61 (s, 3H), 4.50 (septete, 1H), 5.01 (s, 2H), 6.66 (m, 1H), 6.88 (m, 1H), 7.00 (m, 1H), 7.06 (m, 1H), 7.24 (m, 1H), 7.39 (m, 5H), 9.50 (s, 1H). *m/z* 366 $(M+H)^+$

La preparación de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico se describió anteriormente.

La preparación de 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-(3-metil-1,2,4-tiadiazol-2-il)benzamida empleada en **Ejemplos 2f** y **2g** se describe a continuación:

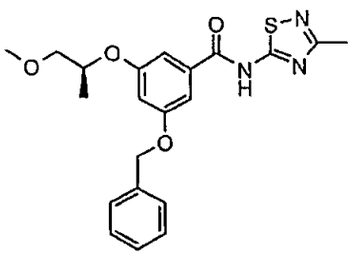
3-Hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-(3-metil-1,2,4-tiadiazol-2-il)benzamida



Una solución de 3-{[(1S)-2-metoxi-(1-metiletil)oxi}-5-{fenilmetiloxi}-N-(3-metil-1,2,4-tiadiazol-2-il)benzamida (9.53 g) y tioanisol (13.9 mL) en ácido trifluoroacético (45 mL) se agitó a temperatura ambiente durante 16 horas. El ácido trifluoroacético se retiró *in vacuo* y el aceite residual se repartió en porciones entre acetato de etilo (100 mL) y solución de bicarbonato de sodio acuoso (300 mL). La capa acuosa se separó, se extrajo con acetato de etilo (2 x 100 mL), y los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y se evaporaron a un residuo, el cual se cromatografió en sílice con 50% acetato de etilo en isohexano como eluyente para producir el compuesto deseado (4.5 g).

^{1}H NMR δ ($CDCl_3$): 1.2 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4-3.6 (m, 2H), 4.6-4.7 (m, 1H), 6.6 (s, 1H), 7.05 (s, 1H), 7.1 (s, 1H), 9.85 (s, 1H), 13.2 (s, 1H). *m/z* 324 $(M+H)^+$

3-{[(1*S*)-2-Metoxi-(1-metiletil)oxi}-5-(fenilmetiloxi}-*N*-(3-metil-1,2,4-tiadiazol-2-il)benzamida

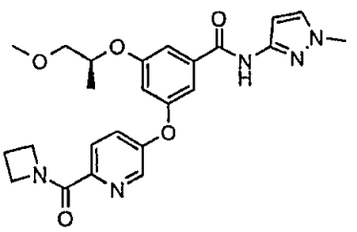


A una solución de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil] oxi}benzoico (15.8 g) en DCM (260 mL) se agregó cloruro de oxalilo (5.24 mL), seguido por DMF (1 gota), y la mezcla se agitó a temperatura ambiente durante 16 horas. El DCM y el exceso de cloruro de oxalilo se retiraron *in vacuo*, el aceite residual se disolvió en DCM (50 mL) y se agregó a una solución de 5-amino-3-metil-1,2,4 tiadiazol (6.05 g) y trietilamina (14.6 mL) en DCM (150 mL) a 0-5°C, y la mezcla se agitó a temperatura ambiente durante 16 horas. El DCM y el exceso de trietilamina

se retiraron *in vacuo*, y el aceite residual se repartió en porciones entre acetato de etilo (250 mL) y 1M ácido clorhídrico (150 mL). La capa de acetato de etilo se separó, se lavó consecutivamente con 1M ácido clorhídrico, solución de bicarbonato de sodio acuoso, y salmuera, se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió en alúmina con acetato de etilo como eluyente, luego en sílice con 30% acetato de etilo en isohexano como eluyente para producir el compuesto deseado (9.6 g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.45 (s, 3H), 3.4 (s, 3H), 3.5-3.6 (m, 2H), 4.55-4.6 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.1 (m, 2H), 7.25 (m, 5H), 10.7 (s, 1H). *m/z* 414 $(M+H)^+$

La síntesis de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil] oxi}benzoico se describe anteriormente.

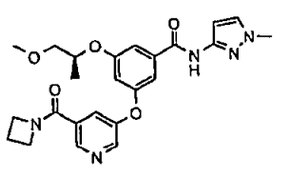
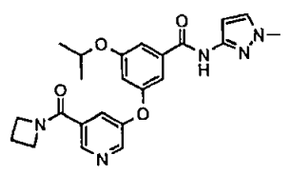
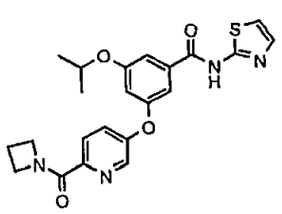
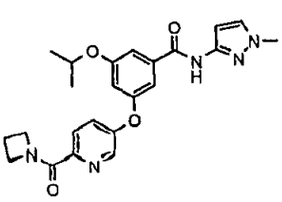
Ejemplo 3: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida

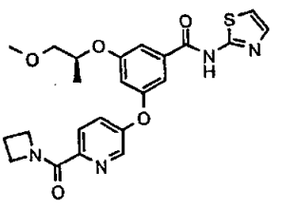
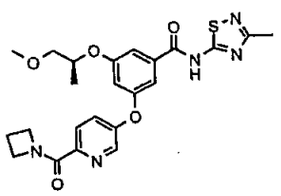
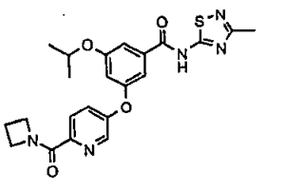


Una mezcla de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-N-(1-metil-1*H*-pirazol-3-il)benzamida (0.2 g, 0.66 mmol), 5-(azetidin-1-ilcarbonil)-2-cloropiridina (158 mg, 0.66 mmol), carbonato de cesio (640 mg, 1.97 mmol) y bromotris(trifenilfosfina)cobre(I) (62 mg, 0.07 mmol) en DMA (5 mL) se agitó en un 'Biotage initiator Microwave' durante 3 horas. La mezcla se dejó alcanzar la temperatura y presión de la sala y se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa de acetato de etilo se separó, se lavó con agua (5 x 50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-5% metanol en acetato de etilo, para producir el compuesto deseado (113 mg). El compuesto se cristalizó

parcialmente de metanol. El material se cristalizó también parcialmente de alcohol isopropílico/isohexano o acetato de etilo/isohexano. Punto de fusión (iniciación de la fusión) 132.7°C. ^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.36 (quintete, 2H), 3.40 (s, 3H), 3.61 - 3.47 (m, 2H), 3.78 (s, 3H), 4.25 (t, 2H), 4.58 (sextete, 1H), 4.72 (t, 2H), 6.80 (t, 2H), 7.11 (s, 1H), 7.31 - 7.27 (m, 2H), 7.40 - 7.35 (m, 1H), 8.12 (d, 1H), 8.32 (s, 1H), 8.32 (s, 1H). *m/z* 466 $(M+H)^+$.

Los siguientes compuestos se sintetizaron en una forma análoga del fenol y la bromopiridina apropiados:

Ejemplo	Estructura	m/z	NMR
3a		466 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.40 (quintete, 2H), 3.41 (s, 3H), 3.49 - 3.62 (m, 2H), 3.80 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.60 (sextete, 1H), 6.80 (m, 2H), 7.10 (t, 1H), 7.27 (t, 1H), 7.30 (d, 1H), 7.62 (t, 1H), 8.51 (d, 1H), 8.61 (s, 2H)
3b		436 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.40 (quintete, 2H), 3.80 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.60 (septete, 1H), 6.74 (t, 1H), 6.80 (s, 1H), 7.07 (s, 1H), 7.07 (s, 1H), 7.30 (d, 1H), 7.62 (t, 1H), 8.51 (s, 1H), 8.61 (s, 2H)
3c		439 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.35 (d, 6H), 2.38 (quintete, 2H), 4.25 (t, 2H), 4.58 (septete, 1H), 4.73 (t, 2H), 6.80 (s, 1H), 6.98 (d, 1H), 7.20 (d, 1H), 7.25 (d, 1H), 7.35 (m, 2H), 8.13 (d, 1H), 8.31 (d, 1H), 12.15 (s, 1H)
3d		436 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.26 (quintete, 2H), 3.69 (s, 3H), 4.18 (t, 2H), 4.49 (septete, 1H), 4.63 (t, 2H), 6.65 (s, 1H), 6.72 (s, 1H), 7.00 (s, 1H), 7.15 (m, 1H), 7.20 (m, 2H), 7.28 (m,

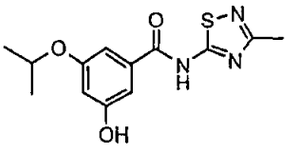
			1H), 8.02 (d, 1H), 8.21 (d, 1H), 8.63 (s, 1H)
3e		469 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.33 (d, 6H), 2.36 (quintete, 2H), 3.38 (s, 3H), 3.48-3.60 (m, 2H), 4.25 (t, 2H), 4.59 (sextete, 1H), 4.72 (t, 2H), 6.88 (m, 1H), 6.97 (d, 1H), 7.19 (d, 1H), 7.28 (m, 2H), 7.38 (m, 2H), 8.12 (d, 1H), 8.30 (d, 1H), 12.30 (s, 1H)
3f		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.29 (quintete, 2H), 2.44 (s, 3H), 3.31 (s, 3H), 3.4 -3.52 (m, 2H), 4.15 (m, 2H), 4.55 (sextete, 1H), 4.65 (t, 1H), 6.80 (m, 1H), 7.25 (m, 2H), 7.40 (m, 1H), 7.60 (m, 1H), 8.00 (d, 1H), 8.21 (s, 1H).
3g		454 $(M+H)^+$	^{1}HNMR δ ($CDCl_3$): 1.30 (d, 6H), 2.29 (quintete, 2H), 2.44 (s, 3H), 4.18 (m, 2H), 4.55 (septete, 1H), 4.65 (t, 1H), 6.74 (m, 1H), 7.18 (m, 1H), 7.30 (m, 1 H), 7.40 (m, 1H), 8.00 (d, 1H), 8.23 (s, 1H), 10.05 (s, 1H)

La preparación de las bromopiridinas requeridas se describe anteriormente.

La preparación de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida, 3-hidroxi-5-[(1-metiletil)oxi]-N-(1-metil-1*H*-pirazol-3-il)benzamida, 3-hidroxi-5-[(1-metiletil)oxi]-*N*-1,3-tiazol-2-ilbenzamida, 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-1,3-tiazol-2-ilbenzamida y 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-(3-metil-1,2,4-tiadiazol-2-il)benzamida se describe anteriormente.

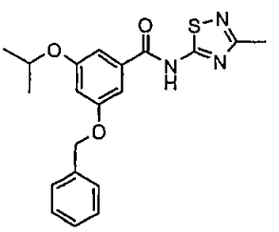
La preparación de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(3-metil-1,2,4-tiadiazol-5-il)benzamida empleada en **Ejemplo 3g** se describe a continuación:

3-Hidroxi-5-[(1-metiletil)oxi]-*N*-(3-metil-1,2,4-tiadiazol-5-il) benzamida



Una solución de 3-[(1-metiletil)oxi]-N-(3-metil-1,2,4-tiadiazol-5-il)-5-[(fenilmetil)oxi]benzamida (33 g, 86 mmol), ácido trifluoroacético (160 mL) y tioanisol (50.5 mL) se agitó a temperatura ambiente durante 48 horas. El TFA se retiró *in vacuo* y el residuo se vertió en solución de bicarbonato de sodio saturado (300 mL) y se extrajo en acetato de etilo (dos veces). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y el disolvente se retiró *in vacuo*. El residuo se trituró con DCM y se lavó con 5% acetato de etilo en isohexano para producir el compuesto deseado (12.8 g). ^1H NMR δ (d_6-DMSO): 1.31 (d, 6H), 2.51 (s, 3H), 4.67 (septete, 1H), 6.58 (s, 1H), 7.08 (s, 1H), 7.24 (s, 1H), 9.88 (s, 1H), 13.25 (bra, 1H). *m/z* 294 $(M+H)^+$

3-[(1-Metiletil)oxi]-*N*-(3-metil-1,2,4-tiadiazol-5-il)-5-[fenilmetil) oxi]benzamida

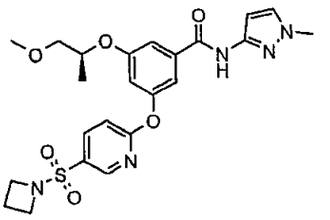


DMF (2 gotas) se agregó a una solución de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico (29.6 g, 0.103 mol) y cloruro de oxalilo (10.78 mL, 0.12 mol) en DCM (500 mL). La mezcla se agitó a temperatura ambiente durante 4 horas y el DCM y el exceso de cloruro de oxalilo se retiró *in vacuo*. El cloruro ácido residual se disolvió en DCM (220 mL) y se agregó gota a gota a 5-amino-3-metil-1,2,4-tiadiazol (12.43 g, 0.108 mol) y trietilamina (30.34 mL, 0.216 mol) en DCM (220 mL), a 0°C. La reacción se dejó calentar y se agitó a temperatura ambiente durante 72 horas. El DCM se retiró *in vacuo*, y el residuo se repartió en porciones entre acetato de etilo (400 mL) y 1N ácido clorhídrico (200 mL). La capa de acetato de

etilo se lavó consecutivamente con bicarbonato de sodio acuoso saturado (200 mL) y salmuera (100 mL), se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 20% acetato de etilo en isohexano, para producir el compuesto deseado (33 g). ^1H NMR δ ($CDCl_3$): 1.32 (d, 6H), 2.31 (s, 3H), 4.51 (septete, 1H), 5.05 (s, 2H), 6.74 (m, 1H), 7.03 (m, 1H), 7.10 (m, 1H), 7.38 (m, 5H), 11.48 (brs, 1H). *m/z* 384 $(M+H)^+$.

La preparación de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico se describe anteriormente.

Ejemplo 4: 3-{[5-(Azetidin-1-ilsulfonil)piridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1H-pirazol-3-il) benzamida

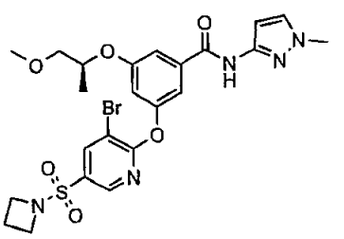


Trietilamina (0.025 mL, 0.18 mmol), luego trietilsilano (0.96 mL, 6.03 mmol) se agregaron a acetato de paladio (II) (12 mg) en DCM (2 mL) y se agitaron bajo argón durante 15 minutos. Se agregó gota a gota 3-{[5-(azetidin-1-ilsulfonil)-3-bromopiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (0.175 g, 0.3 mmol) en DCM (2 mL) y la reacción se agitó a temperatura de la sala durante 24 horas. Se agregó metanol, la reacción se filtró a través de celita y el disolvente se retiró *in vacuo*. Se agregó acetato de etilo (30 mL) y la mezcla se lavó con agua (30 mL), ácido cítrico (30 mL), salmuera (30 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un sólido blanco. Éste se cromatografió en sílice, eluyendo con una gradiente de 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (69 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.09 (quintete, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 3.69 (s, 3H), 3.76 (t, 4H), 4.52 (sextete, 1H), 6.73 (d, 1H), 6.87 (t, 1H), 7.02 (d, 1H), 7.17 (t, 1H), 7.20 (m, 1H), 7.28 (s, 1H), 8.04 (m, 1H), 8.54 (d, 1H), 8.65 (s, 1H). *m/z* 502 $(M+H)^+$

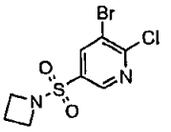
La preparación de 3-{[5-(azetidin-1-ilsulfonil)-3-bromopiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida se describe a continuación:

3-{[5-(Azetidin-1-ilsulfonil)-3-bromopiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



Una mezcla de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (0.2g, 0.66 mmol), 5-(azetidin-1-ilsulfonil)-3-bromo-2-cloropiridina (204 mg, 0.66 mmol) y carbonato de potasio (181 mg, 1.31 mmol) en acetonitrilo (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 2 horas. El disolvente se retiró *in vacuo* y el residuo se disolvió en acetato de etilo y agua, la capa orgánica se lavó con salmuera (50 mL), se secó (MgSO4), se filtró y el disolvente se retiró *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (175 mg). ^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.12 (quintete, 2H), 3.33 (s, 3H), 3.54 - 3.40 (m, 2H), 3.68 (s, 3H), 3.79 (t, 4H), 4.52 (sextete, 1H), 6.73 (d, 1H), 6.89 (t, 1H), 7.18 (t, 1H), 7.21 (d, 1H), 7.30 (t, 1H), 8.27 (d, 1H), 8.38 (d, 1H), 8.77 (s, 1H). *m/z* 580, 582 $(M+H)^+$

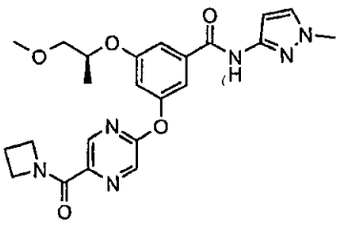
5-(Azetidin-1-ilsulfonil)-3-bromo-2-cloropiridina



Clorhidrato de azetidina (0.32 g, 3.44 mmol) se agregó a una solución de cloruro de 3-bromo-2-cloropiridin-5-sulfonilo (1 g, 3.44 mmol) en DCM (4 mL) y piridina (10 mL) y se agitó a temperatura de la sala durante 22 horas. El disolvente se retiró *in vacuo* y se agregó acetato de etilo (30 mL). La fase orgánica se lavó con 1M ácido clorhídrico (20 mL), agua (20 mL), salmuera (20 mL), se secó (MgSO4), se filtró y el disolvente se retiró *in vacuo* para producir el compuesto deseado (0.4 g).

^{1}H NMR δ ($CDCl_3$): 2.18 (quintete, 2H), 3.83 (t, 4H), 8.26 (s, 1H), 8.66 (s, 1H).

Ejemplo 5: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi)-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



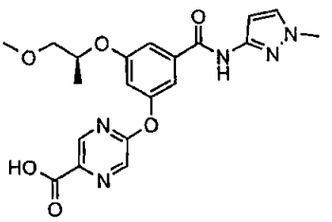
DIPEA (0.28 mL, 1.59 mmol) se agregó a una suspensión de ácido 5-[(3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-{[(1-metil-1H-pirazol-3-il)amino] carbonil}fenil)oxi]pirazin-2-carboxílico (170 mg, 0.4 mmol), HATU (318 mg, 0.84 mmol) y clorhidrato de azetidina (75 mg, 0.8 mmol) en DMF (5 mL) y la mezcla se agitó a temperatura de la sala durante 72 horas. Se agregó acetato de etilo (40 mL) y se lavó con agua (2 x 30 mL), salmuera (30 mL), se secó ($MgSO_4$), se filtró y se redujo *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (48 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.31 (quintete, 2H), 3.32 (s, 3H), 3.41 - 3.55 (m, 2H), 3.71 (s, 3H), 4.19 (t, 2H), 4.52 (m, 1H), 4.60 (t, 2H), 6.72 (s, 1H), 6.86 (m, 1H), 7.16 (m, 1H), 7.20 (m, 1H), 7.28 (m, 1H), 8.25 (s, 1H), 8.52 (s, 1H), 8.52 (s, 1H). *m/z* 467 $(M+H)^+$.

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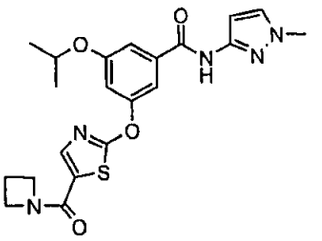
La preparación de ácido 5-[(3-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico se describe a continuación:

Ácido 5-[(3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico



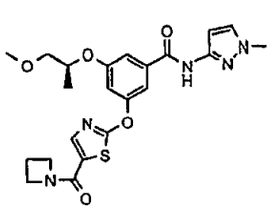
Una mezcla de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (0.226 g, 0.74 mmol), metil 5-cloropirazin-2-carboxilato (192 mg, 1.11 mmol) y carbonato de potasio (205 mg, 1.48 mmol) en acetonitrilo (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 4 horas. El disolvente se retiró *in vacuo* y se agregó (30 mL). La mezcla se acidificó y se extrajo en acetato de etilo (3 x 50 mL), los orgánicos combinados se lavaron con salmuera (30 mL), se secaron (MgSO4), se filtraron y se redujeron *in vacuo* para producir un aceite marrón, el cual era una mezcla del ácido y éster metílico. Monohidrato de hidróxido de litio (78 mg, 1.85 mmol) en agua (2 mL) se agregó a la mezcla de ácido y éster (326 mg, 0.74 mmol) en THF (4 mL) y la mezcla se agitó a temperatura de la sala durante 20 horas. El THF se retiró *in vacuo* y el residuo acuoso se lavó con acetato de etilo (20 mL) para retirar las impurezas, luego se acidificó con 1M ácido cítrico. El producto se extrajo en acetato de etilo (2 x 100 mL) y los orgánicos combinados se lavaron con salmuera (50 mL), se secaron (MgSO4), se filtraron y se redujeron *in vacuo* para producir un sólido amarillo (0.17 g). *m/z* 428 $(M+H)^+$

Ejemplo 6: 3-{[5-(Azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-[(1-metiletil) oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



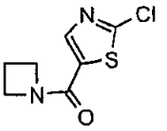
Carbonato de cesio (488 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (187 mg, 0.5 mmol) y 5-(azetidin-1-ilcarbonil)-2-cloro-1,3-tiazol (152 mg, 0.75 mmol) en acetonitrilo (5 mL) y la mezcla agitada se calentó a 160° en un Biotage Initiator Microwave durante 2 horas. La mezcla se enfrió a temperatura y presión de la sala, se vertió en agua (75 mL), luego se extrajo con acetato de etilo (3 x 25 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron a un residuo, el cual se cromatografió en sílice eluyendo con acetato de etilo, para producir el compuesto deseado (142 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.4 (m, 2H), 3.7 (s, 3H), 4.1 - 4.4 (m, 4H), 4.5 (m, 1H), 6.75 (s, 1H), 6.9 (s, 1H), 7.2 (s, 1H), 7.25 (d, 1H), 7.4 (s, 1H) y 8.95 (s, 1H). *m/z* 442 $(M+H)^+$.

El siguiente Ejemplo se preparó en una forma análoga de 5-(azetidin-1-ilcarbonil)-2-cloro-1,3-tiazol y 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-N-(1-metil-1*H*-pirazol-3-il)benzamida.

Ejemplo	Estructura	m/z	NMR
6a		472 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.35 (m, 2H), 3.3 (s, 1H), 3.4-3.55 (m, 2H), 3.7 (s, 3H), 4.1 - 4.4 (m, 4H), 4.5 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.25 (s, 1H), 7.3 (d, 2H), 7.4 (s, 1H) y 8.9 (s, 1H).

La preparación de 5-(azetidin-1-ilcarbonil)-2-cloro-1,3-tiazol se describe a continuación:

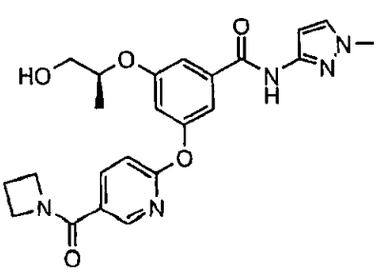
5-(Azetidin-1-ilcarbonil)-2-cloro-1,3-tiazol



A una solución ácido de 2-clorotiazol-5-carboxílico (815 mg, 5 mmol) en diclorometano (10 mL) se agregó lentamente cloruro de oxalilo (0.53 mL, 6 mmol) y luego N,N-dimetilformamida (1 gota) agitando simultáneamente . La mezcla se agitó durante 16 horas, luego de lo cual los orgánicos se retiraron *in vacuo*, y los residuos se destilaron bajo una temperatura fija con tolueno (100ml). El material crudo se disolvió en diclorometano (10 mL) y se agregó lentamente a una suspensión agitada de clorhidrato de azetidina (560 mg, 6 mmol) y trietilamina (2.5 mL, 18 mmol) en diclorometano (25 mL). La mezcla se agitó a temperatura ambiente durante 2 horas antes de retirar los orgánicos *in vacuo*. El residuo se disolvió en acetato de etilo (50 mL) y agua (25 mL), la capa orgánica se lavó con salmuera (25 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice con 40% acetato de etilo en isohexano como eluyente para producir 5-(azetidin-1-ilcarbonil)-2-cloro-1,3-tiazolina. ^{1}H NMR δ ($CDCl_3$): 2.4 (m, 2H), 4.1 - 4.4 (m, 4H), 4.55 (m, 1H), 7.2 (s, 1H) y 7.75 (s, 1H); *m/z* 203 $(M+H)^+$.

La preparación de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil) oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describen anteriormente.

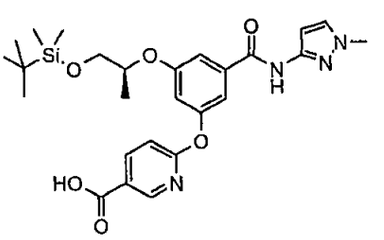
Ejemplo 7: 3-{[5-(Azetidin-1-ilcarbonil)piridin-1-il)oxi}-5-{[(1*S*)-hidroxi-1-metiletil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



Una solución de ácido 6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil) oxi]piridin-3-carboxílico (0.20 g, 0.378 mmol), clorhidrato de azetidina (0.106 g, 0.114 mmol), HATU (0.302 g, 0.794 mmol) y DIPEA (0.39 mL, 0564 mmol) en DMF (7 mL) se agitó a temperatura de la sala de un día para otro. Se agregó 3.5M ácido clorhídrico (0.5 mL) y la solución se dejó agitando durante 20 minutos. La solución se neutralizó con solución de bicarbonato de sodio saturado. Se agregó agua (20 mL) y la solución se extrajo con acetato de etilo (50 mL). La capa de acetato de etilo se lavó con salmuera, se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el producto deseado (27 mg). ^{1}H NMR δ ($CDCl_3$): 1.32 (d, 3H), 2.38 (quintete, 2H), 3.77 (m, 2H), 3.80 (s, 3H), 4.29 (d, 4H), 4.57 (sextete, 1H), 6.81 (d, 1H), 6.91 (t, 1H), 6.99 (d, 1H), 7.27 (m, 2H), 7.38 (m, 1H), 8.42 (d, 1H), 8.86 (s, 1H). *m/z* 452 $(M+H)^+$

La preparación de ácido 6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil] oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil} fenil)oxi]piridin-3-carboxílico se describe a continuación:

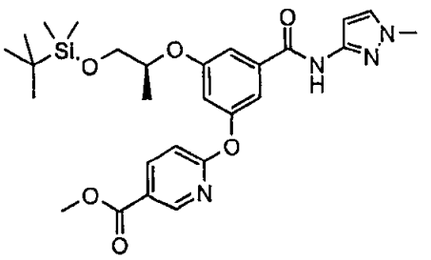
Ácido 6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]piridin-3-carboxílico



Una solución de monohidrato de hidróxido de litio (0.10 g, 4.17 mmol) en agua (15 mL) se agregó a una solución de metil 6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]piridin-3-carboxilato (0.90 g, 1.67 mmol) en THF (30 mL). La mezcla se dejó agitando a temperatura de la sala de un día

para otro. El THF se retiró *in vaccuo* y la solución resultante se repartió en porciones entre agua (50 mL) y acetato de etilo (75 mL), luego la capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$). La capa acuosa se tomó entonces a pH 7 mediante la adición de 1N ácido clorhídrico (5.2 mL) y se extrajo con acetato de etilo (75 mL). La capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$). Las capa de acetato de etilo se combinaron y se evaporaron para proporcionar el producto requerido (0.84 g). ^{1}H NMR δ ($CDCl_3$): 0.05 (d, 6H), 0.88 (s, 9H), 1.36 (d, 3H), 3.70-3.88 (m, 5H), 4.52-4.61 (sex, 1H), 6.98 (d, 2H), 7.01 (d, 1H), 6.28 (s, 1H), 7.44 (s, 1H), 7.57 (s, 1H), 8.04 (m, 1H), 8.72 (s, 1H), 10.62 (s, 1H). *m/z* 527 $(M+H)^+$

Metil 6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil) oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil)fenil)oxi]piridin-3-carboxilato

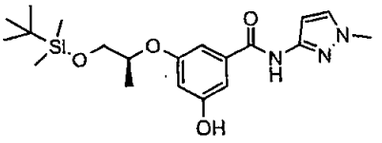


Una solución de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1.00 g, 2.47 mmol), metil 6-cloronicotinato (0.450 g, 2.60 mmol), y carbonato de cesio (1.204 g, 3.71 mmol) en acetonitrilo (15 mL) se calentó a 160°C empleando calentamiento de microondas durante 90 minutos. El acetonitrilo se retiró *in vaccuo* y el aceite residual se repartió en porciones entre agua (50 mL) y acetato de etilo (75 mL). La capa de acetato de etilo se separó, se lavó con salmuera, se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el compuesto deseado (0.977 g).

^{1}H NMR δ ($CDCl_3$): 0.05 (d, 6H), 0.87 (s, 9H), 1.34 (d, 3H), 3.54 (m, 3H), 3.79 (s, 3H), 3.93 (s, 3H), 4.59 (sextete, 1H), 6.79 (d, 1H), 6.92 (t, 1H), 6.96

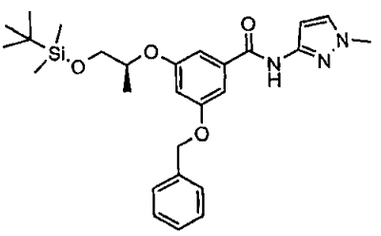
(s, 1H), 6.99 (s, 1H), 7.20 (t, 1H), 7.27 (d, 1H), 7.33 (t, 1H), 8.28 (d, 1H), 8.31 (d, 1H), 8.39 (s, 1H), 8.82 (d, 1H). *m/z* $(M+H)^+$ 541

3-[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



3-[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (1.8 g, 3.64 mmol) se disolvió en metanol (50 mL) y el matraz se vació y se purgó con nitrógeno (3 veces). 10% Paladio sobre carbón (0.2 g) se agregó y el matraz se volvió a vaciar y, finalmente, se purgó con gas hidrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 16 horas hasta completarse. La mezcla de reacción se vació y se purgó con nitrógeno (3 veces). El catalizador se extrajo completamente por filtración, y el filtrado se concentró *in vacuo* para producir el compuesto deseado (1.45 g). ^{1}H NMR δ (d_6-DMSO): 0.02 (d, 6H), 0.83 (s, 9H), 1.18 (d, 3H), 3.66 (m, 2H), 3.72 (s, 3H), 4.51 (m, 1H), 6.42 (m, 1H), 6.52 (m, 1H), 6.90 (s, 1H), 7.02 (s, 1H), 7.55 (m, 1H), 9.58 (br s, 1H), 10.59 (br s, 1H). *m/z* 406 $(M+H)^+$

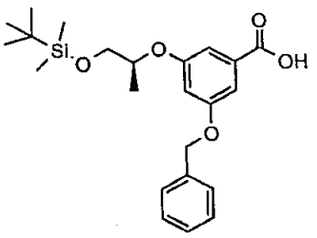
3-[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida



DIPEA (4.06 g, 23.4 mmol) se agregó a una suspensión de ácido 3-[((1S)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-[(fenilmetil) oxi]benzoico (2.43 g, 5.84 mmol), 3-amino-1-metilpirazol (0.85 g, 8.76 mmol) y HATU (4.66 g, 12.3 mmol) en DMF (50 mL) y se agitó a temperatura ambiente durante 16 horas. La mezcla resultante se redujo

parcialmente *in vacuo*, se vertió en agua (100 mL) y se extrajo con éter dietílico (2 x 50 mL). Los extractos se lavaron con agua y salmuera, luego se secaron ($MgSO_4$), se filtraron y se redujeron a una goma opaca, que se cristalizó parcialmente. El producto crudo se purificó por cromatografía en columna, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto del título como un aceite incoloro (1.87g). ^{1}H NMR δ (d_6-DMSO): 0.02 (d, 6H), 0.84 (s, 9H), 1.21 (d, 3H), 3.68 (d, 2H), 3.76 (s, 3H), 4.58 (m, 1H), 5.13 (s, 2H), 6.56 (m, 1H), 6.70 (m, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.29- 7.46 (m, 5H), 7.57 (m, 1H), 10.74 (br s, 1H). *m/z* 496 $(M+H)^+$.

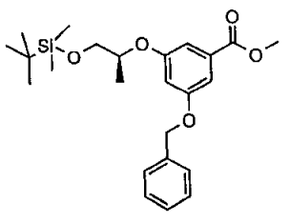
Ácido 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico



Metil 3-[((1*S*)-1-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoato (3.0 g, 6.98 mmol) se disolvió en THF (50 mL) y agua (10mL), y se agregó monohidrato de hidróxido de litio (586 mg, 13.95 mmol). La mezcla resultante se calentó agitando simultáneamente a 45°C durante 2 horas, luego a temperatura ambiente durante 16 horas, y a 45°C durante 4 horas más. Se agregó agua (40 mL) y el disolvente se retiró *in vacuo*. La solución resultante se acidificó cuidadosamente con 1M ácido cítrico (2 equivalentes), se lavó con agua y salmuera, luego se secó ($MgSO_4$), se filtró y se evaporó *in vacuo* para producir el compuesto del título como una goma incolora (2.58 g).

^{1}H NMR δ (d_6-DMSO): 0.02 (d, 6H), 0.84 (s, 9H), 1.17 (d, 3H), 3.66 (m, 2H), 4.43 (m, 1H), 5.05 (s, 2H), 6.56 (br s, 1H), 7.10 (br s, 1H), 7.17 (br s, 1H), 7.25-7.44 (m, 5H), 7.60 (br s, 1H).

Metil 3-[((1*S*)-2-{[1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoato

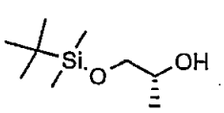


(2*R*)-1-{[(1,1-Dimetiletil)(dimetil)silil]oxi}propan-2-ol (3.31 g, 17.4 mmol) se agregó a una solución de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (3.00 g, 11.6 mmol) en THF (50 mL) a 0°C, seguido por la adición de trifenilfosfina (4.57 g, 17.4 mmol) luego DIAD (3.43 mL, 17.4 mmol), y la reacción se calentó a temperatura de la sala y se agitó durante 16 horas. La reacción se extinguió con agua (100 mL) y éter dietílico (400 mL), y la capa orgánica se separó, luego se secó ($MgSO_4$) y se evaporó. La purificación por cromatografía en columna, eluyendo con 1:15 a 1:5 acetato de etilo:hexano, produjo el compuesto del título como un aceite incoloro (4.00 g, 80%).

^{1}H NMR δ ($CDCl_3$): 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.29 (d, 3H), 3.63 (dd, 1H), 3.78 (dd, 1H), 3.92 (s, 3H), 4.44 (m, 1H), 5.08 (s, 2H), 6.77 (m, 1H), 7.40 (m, 7H).

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente.

(2*R*)-1-{[(1,1-Dimetiletil)(dimetil)silil]oxi}propan-2-ol



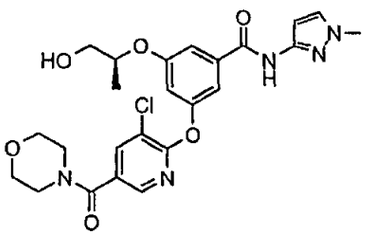
Cloruro de *terc*-butil(dimetil)sililo (5.90 g, 39.5 mmol) se agregó a una solución de (2R)-propano-1,2-diol (3.00 g, 39.5 mmol) en DCM (100 mL), seguido por diisopropiletilamina (7.10 g, 55.3 mmol), y la reacción se agitó bajo argón durante 72 horas. La reacción se diluyó con éter dietílico (500 mL) y agua (140 mL), y la capa orgánica se separó, luego se secó ($MgSO_4$),

se filtró y se evaporó. La purificación por cromatografía en columna, eluyendo con 1:15 a 1:10 acetato de etilo: hexano, produjo el compuesto del título como un aceite incoloro (6.00 g, 80%).

^{1}H NMR δ ($CDCl_3$): 0.10 (m, 6H), 0.92 (s, 9H), 1.14 (d, 3H), 2.42 (d, 1H), 3.38 (dd, 1H), 3.60 (dd, 1H), 3.82 (m, 1H).

Los datos correspondieron a los divulgados en la literatura (*J. Org. Chem.*, **1998**, 53, 2300).

Ejemplo 8: 3-{[-Cloro-5-(morfolin-4-ilcarbonil)piridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida

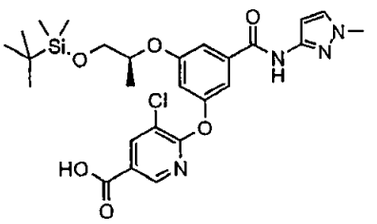


Una solución de ácido 5-cloro-6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]piridin-3-carboxílico (0.15 g, 0.267 mmol), morfolina (0.07 mL, 0.803 mmol), HATU (0.213 g, 0.560 mmol) y DIPEA (0.15 mL, 0.861 mmol) en DMF (7 mL) se agitó a temperatura de la sala durante 2 días. Se agregó agua (20 mL) y la solución se extrajo con acetato de etilo (50 mL). La capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 1% metanol en acetato de etilo. Se agregó 3.5M ácido clorhídrico (0.5 mL) a una solución del sólido residual tomado en metanol (5 mL) y se puso a agitar a temperatura de la sala durante 20 minutos. La solución se neutralizó con solución de bicarbonato de sodio saturado y se retiró el metanol *in vaccuo* y la solución residual se repartió en porciones entre agua (20 mL) y acetato de etilo. La capa de acetato de etilo se separó y se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para producir el producto deseado (34 mg). ^{1}H NMR δ (d6-DMSO): 1.28 (d, 3H), 3.58 (m, 10H), 3.81 (s, 3H), 4.61 (sextete, 1H), 4.89 (t, 1H), 6.60 (d, 1H), 7.03 (t,

1H), 7.41 (s, 1H), 7.54 (s, 1H), 7.63 (d, 1H), 8.20 (q, 2H), 10.84 (s, 1H). *m/z* 516 $(M+H)^+$

La preparación de ácido 5-cloro-6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil) silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil} fenil)oxi]piridin-3-carboxílico se describe a continuación:

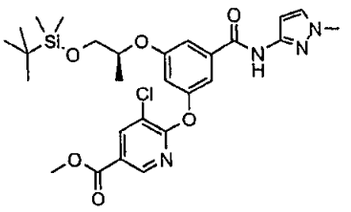
Ácido 5-cloro-6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil) oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxiipiridin-3-carboxílico



A una solución de metil 5-cloro-6-[(3-[((1*S*)-2-{[(1,1-dimetiletil) (dimetil)silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il) amino]carbonil}fenil)oxi]piridin-3-carboxilato (1.2 g, 2.09 mmol) en THF (50 mL) se agregó una solución de monohidrato de hidróxido de litio (0.219 g, 5.22 mmol) en agua (30 mL). La mezcla se dejó agitando bajo temperatura de la sala de un día para otro. El THF se retiró *in vacuo* y la solución resultante se repartió en porciones entre agua (50 mL) y acetato de etilo (75 mL), y la capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$). La capa acuosa se ajustó entonces a pH 7 mediante la adición de 1N ácido clorhídrico (5.2 mL) y se repartió en porciones entre acetato de etilo (75 mL). La capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$). Las capas de acetato de etilo se combinaron y se evaporaron para proporcionar el producto requerido (1.1 g).

^{1}H NMR δ (d_6-DMSO): 0.01 (d, 6H), 0.82 (s, 9H), 1.22 (d, 3H), 3.73 (m, 2H), 3.76 (s, 3H), 4.55 (sextete, 1H), 6.55 (d, 1H), 6.90 (t, 1H), 7.30 (s, 1H), 7.44 (s, 1H), 7.58 (d, 1H), 8.36 (d, 1H), 8.19 (d, 1H), 8.51 (s, 1H). *m/z* $(M+H)^+$ 562.

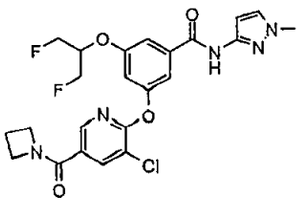
Metil 5-cloro-6-[(3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil) oxiipiridin-3-carboxilato



Una solución de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1.0 g, 2.47 mmol), etil 5,6-dicloronicotinato (0.57 g, 2.59 mmol), y carbonato de potasio (0.855 g, 6.14 mmol) en acetonitrilo (15 mL) se calentó a 160°C durante 4 horas empleando calefacción de microondas. El acetonitrilo se retiró *in vaccuo* y el aceite residual se repartió en porciones entre agua (50 mL) y acetato de etilo (75 mL). La capa de acetato de etilo se separó, se lavó con salmuera, se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en hexano para producir el compuesto deseado (1.1 g). Los datos analíticos indicaron que la transesterificación había ocurrido en alguna etapa en el procedimiento para proporcionar el éster metílico. ^{1}H NMR δ ($CDCl_3$): 0.05 (d, 6H), 0.87 (s, 9H), 1.30 (d, 3H), 3.72 (s, 3H), 3.73 (m, 1H), 3.93 (s, 3H), 4.47 (sextete, 1H), 6.80 (d, 1H), 6.93 (t, 1H), 7.19 (t, 1H), 7.25 (d, 1H), 7.26 (s, 1H), 7.34 (t, 1H), 8.35 (d, 1H), 8.61 (d, 1H), 8.97 (s, 1H); *m/z* $(M+H)^+$ 575

La preparación de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describe anteriormente.

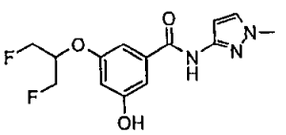
Ejemplo 9: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



Una mezcla de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (200 mg, 0.64 mmol), 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (164 mg, 0.71 mmol) y carbonato de potasio (178 mg, 1.28 mmol) en acetonitrilo (5 mL) se agitó en un 'Biotage initiator Microwave' a 120°C durante 4 horas. El disolvente se retiró *in vacuo* y el residuo se repartió en porciones entre acetato de etilo y agua (100 mL), la capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (237 mg).
^{1}H NMR δ ($CDCl_3$): 2.39 (quintete, 2H), 3.74 (s, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.63 (m, 2H), 4.74 (m, 3H), 6.81 (s, 1H), 7.01 (s, 1H), 7.29 (m, 1H), 7.31 (s, 1H), 7.42 (s, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 9.26 (s, 1H). *m/z* 506 $(M+H)^+$.

La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describe anteriormente. La preparación de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describe a continuación:

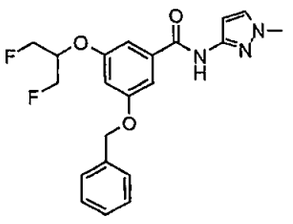
3-{[2-Fluoro-1-(fluorometil)etil]oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



Una solución de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (2.46 g, 6.13 mmol) y 10% en peso de paladio sobre carbón (0.246 g) en etanol (100 mL) se dejó agitando a temperatura de la sala, bajo una atmósfera de hidrógeno de un día para otro. La solución se filtró a través de Celite® y la torta se lavó con metanol (100 mL). La solución se evaporó para producir el compuesto deseado (1.78 g). ^{1}H NMR δ (d_6-DMSO): 3.78 (s, 3H), 4.72 (m, 4H), 4.97 (m, 1H), 6.57 (d, 2H), 7.03 (s, 1H), 7.16 (s, 1H), 7.59 (s, 1H). *m/z* 312 $(M+H)^+$.

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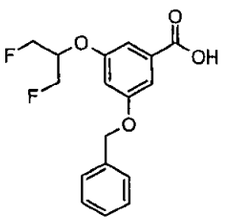
3-{[2-Fluoro-1-(fluorometil)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida



Una solución de ácido 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi]benzoico (3.00 g, 9.31 mmol), 3-amino-1-metilpirazol (1.83 g, 18.6 mmol), HATU (4.60 g, 12.1 mmol) y DIPEA (3.25 mL, 18.6 mmol) en DMF (12 mL) se agitó a temperatura de la sala de un día para otro. Se agregó agua (150 mL) y la solución se repartió en porciones con acetato de etilo (250 mL). La capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el producto deseado (2.46 g).

^{1}H NMR δ ($CDCl_3$): 3.69 (s, 3H), 4.57 (m, 5H), 5.00 (s, 2H), 6.70 (t, 1H), 6.74 (d, 1H), 7.01 (t, 1H), 7.08 (t, 1H), 7.21 (d, 1H), 7.30 (m, 5H), 8.68 (s, 1H); *m/z* 402 $(M+H)^+$.

Ácido 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi]benzoico

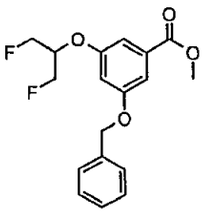


Una solución de monohidrato de hidróxido de litio (2.32 g, 55.1 mmol) en agua (100 mL) se agregó a una solución de metil 3-{[2-fluoro-1-(fluorometil) etil]oxi}-5-[(fenilmetil)oxi]benzoato (7.41 g, 22.0 mmol) en THF (200 mL) y la mezcla se dejó agitando a temperatura de la sala de un día para otro. El THF se retiró *in vacuo* y la solución resultante se repartió en porciones entre agua (100 mL) y acetato de etilo (250 mL). La capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$). La capa

acuosa se ajustó entonces a pH 7 mediante la adición de 1M ácido clorhídrico y se extrajo con acetato de etilo (75 mL). La capa de acetato de etilo se separó, se lavó con salmuera y se secó ($MgSO_4$). La capa de acetato de etilos se combinó y se evaporó para proporcionar el producto requerido (6.404 g).

^{1}H NMR δ (d_6-DMSO): 4.74 (m, 4H), 5.08 (s, 2H), 6.67 (s, 1H), 6.67 (s, 1H), 7.23 (s, 1H), 7.37 (m, 5H). *m/z* 231 $(M-H)^-$.

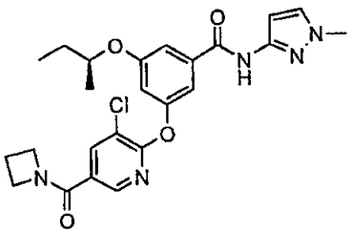
Metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi] benzoato



DIAD (7.63 mL, 38.7 mmol) se agregó gota a gota a una solución de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (5.00 g, 19.4 mmol), 1,3-difluoropropan-2-ol (3 mL, 38.7 mmol), y trifenilfosfina (10.16 g, 38.7 mmol) en THF (100 mL) bajo una atmósfera inerte a 0°C. Se dejó que la solución alcanzara la temperatura de la sala y se dejó agitando durante 2 días. El THF se retiró *in vacuo* y el aceite residual se suspendió con una mezcla de 20% acetato de etilo en isohexano. Luego de dejar agitar durante 90 minutos, la mezcla se filtró y el filtrado se evaporó. El aceite residual se cromatografió en sílice, eluyendo con 30% acetato de etilo en isohexano, para producir el compuesto deseado (7.41g). ^{1}H NMR δ (d_6-DMSO): 3.85 (s, 3H), 4.71 (m, 4H), 5.03 (m, 1H), 5.17 (s, 2H), 7.01 (t, 1H), 7.20 (m, 2H), 7.40 (m, 5H). *m/z* 335 $(M-H)^-$.

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describe anteriormente.

Ejemplo 10: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida

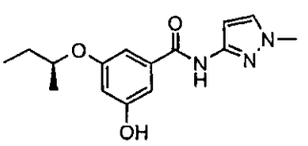


Una solución de 3-hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (116 mg, 0.4 mmol) y la 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (111 mg, 0.48 mmol) en acetonitrilo (2 mL), que contenía carbonato de potasio (111 mg, 0.8 mmol), se calentó agitando simultáneamente en el reactor microondas durante 6 horas a 160°C. La mezcla de reacción se filtró t el filtrado se evaporó a sequedad bajo presión reducida y se purificó por cromatografía en sílice, eluyendo con 50-100% acetato de etilo en hexano, para proporcionar el producto requerido (177 mg).

^{1}H NMR δ ($CDCl_3$): 0.91 (t, 3H), 1.25 (d, 3H), 1.52 - 1.75 (m, 2H), 2.32 (quintete, 2H), 3.72 (s, 3H), 4.17 (t, 2H), 4.25 - 4.34 (m, 3H), 6.73 (d, 1H), 6.81 (t, 1H), 7.12 (s, 1H), 7.21 (d, 1H), 7.24 (s, 1H), 8.09 (d, 1H), 8.18 (d, 1H), 8.54 (s, 1H); *m/z* 484 $(M+H)^+$.

La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describió anteriormente. La preparación de 3-hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describe a continuación:

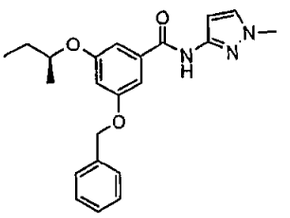
3-Hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



Una solución de 3-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (900 mg) en THF (5 mL) y etanol (5 mL) que contenía 10% paladio sobre carbón se agitó bajo una atmósfera de hidrógeno de un día para otro. Se retiró el paladio sobre carbón mediante filtración y el filtrado se evaporó bajo presión reducida para producir el

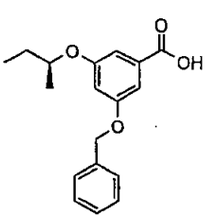
compuesto requerido como un sólido blanco (683 mg). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.27 (d, 3H), 1.54 - 1.80 (m, 2H), 3.79 (s, 3H), 4.31 (q, 1H), 6.57 (t, 1H), 6.81 (d, 1H), 6.96 (s, 1H), 6.98 (s, 1H), 7.30 (s, 1H), 7.57 (s, 1H), 8.84 (s, 1H); *m/z* 290$(M+H)^+$.

3-{[(1*S*)-1-Metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil) oxi]benzamida



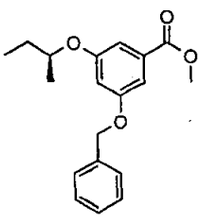
HATU (1.19 g, 3.13 mmol) se agregó a ácido 3-{[(1*S*)-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoico (750 mg, 2.5 mmol) y 3-amino-l metil pirazol (291 mg, 3 mmol) en DMF (5 mL), seguido por la adición de DIPEA (0.807 mL, 6.25 mmol), y la reacción se agitó durante 16 horas. La mezcla de reacción se agregó a acetato de etilo (30 mL), se lavó con agua (10 mL), 2N ácido cítrico (10 mL), bicarbonato de sodio acuoso saturado (10 mL) y salmuera (10 mL), luego se secó ($MgSO_4$), se filtró y se evaporó a un residuo gomoso. El residuo se tomó en 50% éter en acetato de etilo (50 mL), se lavó con 2N ácido clorhídrico (10 mL), agua (10 mL), bicarbonato de sodio acuoso saturado (10 mL) y salmuera (10 mL), luego se secó ($MgSO_4$), se filtró y se evaporó a una espuma (900 mg), la cual se utilizó sin purificación posterior en el siguiente paso. ^{1}H NMR o ($CDCl_3$): 0.96 (t, 3H), 1.28 (d, 3H), 1.51-1.80 (m, 2H), 3.78 (s, 1H), 4.31 (q, 1H), 5.06 (s, 2H), 6.68 (t, 1H), 6.82 (d, 1H), 7.00 (s, 1H), 7.06 (s, 1H), 7.29 (s, 3H), 7.31 - 7.47 (m, 5H), 8.63 (s, 1H); *m/z* 380 $(M+H)^+$.

Ácido 3-{[(1*S*)-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoico



Metil 3-{[(1*S*)-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoato (14.87 g, 47.36 mmol) se agitó vigororosamente en una mezcla de 1M hidróxido de sodio (120 mL) acuoso y THF a aproximadamente 45°C durante 4 horas. El grueso del THF se retiró bajo presión reducida y la solución resultante se repartió en porciones entre agua y éter dietílico. La fase acuosa se acidificó con 2M ácido clorhídrico y luego se extrajo con acetato de etilo. Los orgánicos se secaron ($MgSO_4$) y se concentraron *in vacuo* para producir un sólido blanco (11.5 g). ^{1}H NMR δ ($CDCl_3$): 0.90 (t, 3H), 1.20 (d, 3H), 1.49 - 1.69 (m, 2H), 4.33 - 4.46 (m, 1H), 5.12 (s, 2H), 6.75 - 6.79 (m, 1H), 6.99 - 7.03 (m, 1H), 7.06 - 7.11 (m, 1H), 7.26 - 7.47 (m, 5H).

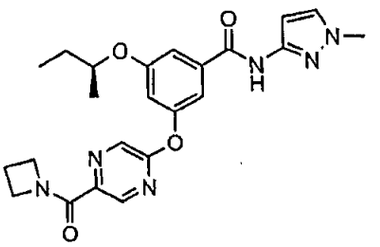
Metil 3-{[(1*S*)-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoato



Una solución de DIAD (16.6 mL, 84.0 mmol) en THF seco (100 mL) se agregó gota a gota a una mezcla enfriada (baño helado) de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (14.5 g, 56.2 mmol); R-(-)-sec-butanol (5 g, 67.0 mmol) y trifenilfosfina soportada en un sólido (28 g, de 3 mmol por g de carga, 84.0 mmol) en THF seco (400 mL), manteniendo simultáneamente la temperatura por debajo de 10°C. La mezcla se dejó agitando durante 3 horas, luego se diluyó con éter dietílico (800 mL) y se filtró. El retiro del disolvente produjo un aceite de color pálido, el cual se purificó por cromatografía en columna en sílice, eluyendo con 25% acetato de etilo en hexano; para producir el producto deseado (14.87 g).
^{1}H NMR δ ($CDCl_3$): 0.99 (t, 3H), 1.28 (d, 3H), 1.53 - 1.80 (m, 2H), 3.89 (s, 3H), 4.25 - 4.42 (m, 1H), 5.07 (s, 2H), 6.68 - 6.81 (m, 1H), 7.17 - 7.53 (m, 7H); *m/z* 313 $(M-H)^-$.

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente.

Ejemplo 11 : 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida

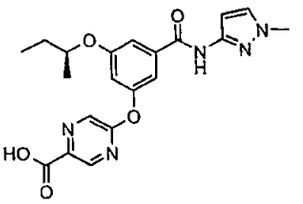


HATU (34 mg, 0.89 mmol) se agregó a ácido 5-[(3-{[(1*S*)-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil) oxi]pirazin-2-carboxílico (190 mg, 0.4 mmol), y se agregó clorhidrato de azetidina (84 mg, 0.89 mmol) en DMF (5 mL). DIPEA (0.311 mL, 1.79 mmol), y la reacción se agitó durante 16 horas. La mezcla de reacción se agregó a acetato de etilo (20 mL), se lavó con agua (10 mL), 2N ácido cítrico (10 mL), bicarbonato de sodio acuoso saturado (10 mL) y salmuera (10 mL), luego se secó ($MgSO_4$), se filtró y se evaporó bajo presión reducida a un residuo gomoso. El residuo se purificó por cromatografía en sílice, eluyendo con 50-100% acetato de etilo en hexano, para producir una goma, la cual se tomó en 50% acetato de etilo en éter y se lavó dos veces con agua, salmuera (10 mL), luego se secó ($MgSO_4$) para producir el producto deseado como una espuma (58 mg).

^{1}H NMR δ ($CDCl_3$): 0.91 (t, 3H), 1.25 (d, 3H), 1.51 - 1.75 (m, 2H), 2.31 (quintete, 2H), 3.72 (s, 3H), 4.19 (t, 2H), 4.29 (q, 1H), 4.62 (t, 2H), 6.73 (d, 1H), 6.80 (t, 1H), 7.13 (t, 1H), 7.21 (d, 1H), 7.23 (t, 1H), 8.26 (s, 1H), 8.52 (s, 1H), 8.79 (s, 1H); *m/z* 451 $(M+H)^+$

La preparación de ácido 5-[(3-{[(1*S*)-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico se describe a continuación:

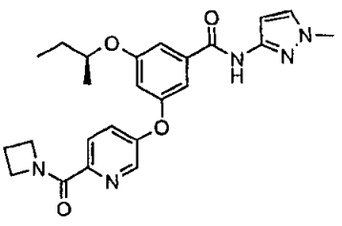
Ácido 5-[(3-{[(1*S*)-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino] carbonil}fenil)oxi]pirazin-2-carboxílico



Una solución de 3-hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (116 mg, 0.4 mmol) y el metil 5-cloropirazin-2-carboxilato (83 mg, 0.48 mmol) en acetonitrilo (2 mL), que contenía carbonato de potasio (111 mg, 0.8 mmol), se calentó agitando simultáneamente en el microondas durante 6 horas a 160°C. LC-MS analítica mostró la formación del ácido, pero no de éster. La mezcla de reacción se disolvió en agua (10 mL), se acidificó con 2N ácido cítrico y se extrajo con acetato de etilo (5 x 20 mL), se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a sequedad bajo presión reducida para proporcionar el producto deseado (190 mg), el cual se utilizó sin purificación posterior en el siguiente paso. m/z 412 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describió anteriormente.

Ejemplo 12: 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-Pirazol-3-il)benzamida

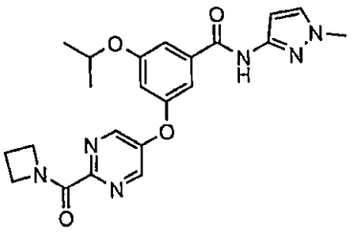


Una mezcla de 3-hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (0.116 g, 0.4 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (116 mg, 0.48 mmol), carbonato de cesio (392 mg, 1.2 mmol) y bromotris(trifenilfosfina)cobre(I) (38 mg, 0.04 mmol) en DMA (5 mL) se agitó en el reactor de microondas a 160°C durante 4 horas. El producto se disolvió en acetato de etilo (20 mL) y agua (15 mL), y las capas se separaron. La capa orgánica se lavó con salmuera (50 mL), se secó

($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-5% metanol en acetato de etilo, y luego se volvió a pasar por la columna en sílice, eluyendo con una gradiente de 0-5% metanol en DCM, para producir el compuesto deseado como una espuma blanca, la cual se cristalizó luego de reposar. El material se trituró con 50% acetato de etilo en hexano para proporcionar el producto requerido como un sólido blanco (95 mg). ^{1}H NMR δ ($CDCl_3$): 0.90 (t, 3H), 1.23 (d, 3H), 1.51 - 1.72 (m, 2H), 2.28 (quintete, 2H), 3.73 (s, 3H), 4.18 (t, 2H), 4.28 (q, 1H), 4.64 (t, 2H), 6.67 (t, 1H), 6.72 (d, 1H), 6.99 (s, 1H), 7.15 (s, 1H), 7.22 (d, 1H), 7.31 (d, 1H), 8.04 (d, 1H), 8.26 (s, 1H), 8.41 (s, 1H); *m/z* 450 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*S*)-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describieron anteriormente.

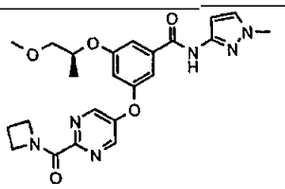
Ejemplo 13: 3-{[2-(Azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-[(1-metiletil) oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



Una mezcla de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (250 mg, 0.91 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopirimidina (242 mg, 1.0 mmol), carbonato de cesio (886 mg, 2.72 mmol) y bromotris(trifenilfosfina)cobre(I) (423 mg, 0.45 mmol) en DMA (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 4 horas. La mezcla se agregó a acetato de etilo (50 mL) y agua (50 mL), la capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite marrón. El residuo se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en

acetato de etilo, para producir el compuesto deseado (199 mg). ^{1}H NMR δ ($CDCl_3$): 1.39 (d, 6H), 2.40 (quintete, 2H), 3.82 (s, 3H), 4.35 (t, 2H), 4.62 (mult, 1H), 4.68 (t, 2H), 6.79 (s, 1H), 6.84 (s, 1H), 7.20 (s, 1H), 7.33 (mult, 2H), 8.60 (s, 2H), 8.97 (s, 1H); *m/z* 437 $(M+H)^+$.

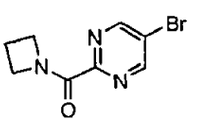
El siguiente compuesto se sintetizó en una forma análoga de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida.

Ejemplo	Estructura	m/z	NMR
13a		467 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.37 (quintete, 2H), 3.41 (s, 3H), 3.48 - 3.60 (m, 2H), 3.78 (s, 3H), 4.30 (t, 2H), 4.58 (mult, 1H), 4.64 (t, 2H), 6.80 (d, 1H), 6.83 (t, 1H), 7.19 (s, 1H), 7.30 (d, 1H), 7.33 (s, 1H), 8.55 (s, 2H), 8.93 (s, 1H)

La preparación de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describieron anteriormente.

La preparación de 2-(azetidin-1-ilcarbonil)-5-bromopirimidina se describe a continuación:

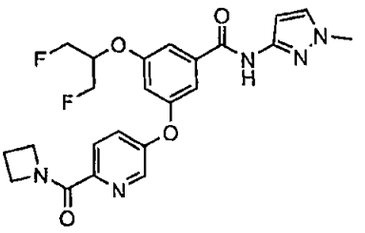
2-(Azetidin-1-ilcarbonil)-5-bromopirimidina



Cloruro de oxalilo (1.50 mL, 16.8 mmol), luego DMF (2 gotas), se agregaron a una mezcla de ácido 5-bromopirimidin-2-carboxílico (preparado de acuerdo con el procedimiento de la literatura descrito en WO 2005/028452) (2.86 g, 14.0 mmol) en DCM (40 mL). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas, los volátiles se retiraron *in vacuo*, y el residuo se disolvió en DCM (40 mL). Se agregaron

clorhidrato de azetidina (1.44 g, 15.4 mmol), seguido por trietilamina (4.29 mL, 30.8 mmol), y la mezcla se agitó a temperatura de la sala durante 72 horas. La mezcla se concentró *in vacuo*, y se agregó acetato de etilo (100 mL) al residuo. Los orgánicos se lavaron con agua (100 mL), solución de cítrico (50 mL), solución de bicarbonato de sodio saturado (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir un sólido amarillo, el cual se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (0.86 g). ^{1}H NMR δ ($CDCl_3$): 2.39 (quintete, 2H), 4.32 (t, 2H), 4.63 (t, 2H), 8.92 (s, 2H); *m/z* 242, 244 $(M+H)^+$.

Ejemplo 14: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



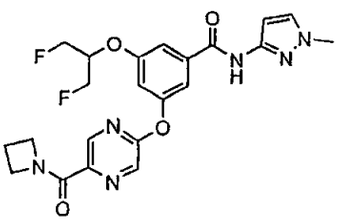
Una mezcla de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (100 mg, 0.32 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (86 mg, 0.35 mmol), carbonato de cesio (209 mg, 0.64 mmol) y bromotris(trifenilfosfina)cobre(I) (150 mg, 0.16 mmol) en DMA (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 3 horas. La mezcla de reacción se agregó a acetato de etilo (50 mL) y agua (50 mL), la capa orgánica se lavó con salmuera (50 mL), se secón ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite marrón. El residuo se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir un aceite incoloro, el cual pareció ser una mezcla de producto y producto eliminado (3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[1-(fluorometil)etenil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida). Esta mezcla se disolvió en cloroformo (5 mL), se agregó TFA (0.5 mL) y la mezcla se agitó durante 2 horas. Se observó la degradación

completa del producto eliminado mediante LCMS, y la mezcla se concentró *in vacuo*, luego se agregó agua. La mezcla se neutralizó y se extrajo en acetato de etilo (2 x 30 mL), se lavó con salmuera (30 mL), se secó ($MgSO_4$), se filtró y se redujo para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (13 mg).

^{1}H NMR δ ($CDCl_3$): 2.29 (quintete, 2H), 3.76 (s, 3H), 4.19 (t, 2H), 4.55 (mult, 2H), 4.67 (mult, 5H), 6.72 (s, 1H), 6.80 (mult, 1H), 7.09 (s, 1H), 7.25 (mult, 2H), 7.32 (mult, 1H), 8.06 (d, 1H), 8.26 (d, 1H), 8.43 (s, 1H); *m/z* 472 $(M+H)^+$.

La preparación de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describieron anteriormente.

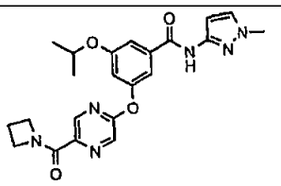
Ejemplo 15: 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



DIPEA (0.45 mL, 2.58 mmol) se agregó a una mezcla de ácido 5-[(3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico (0.28 g, 0.65 mmol), clorhidrato de azetidina (121 mg, 1.29 mmol) y HATU (516 mg, 1.36 mmol) en DMF (5 mL) y se agitó a temperatura de la sala durante 72 horas. Se agregó acetato de etilo (40 mL), y los orgánicos se lavaron con agua (2 x 30 mL), salmuera (30 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (109 mg). ^{1}H NMR δ ($CDCl_3$): 2.32 (quintete, 2H), 3.70 (s, 3H), 4.19 (t, 2H), 4.54 - 4.72 (m, 7H), 6.73 (s, 1H), 6.93 (t, 1H), 7.22 (d

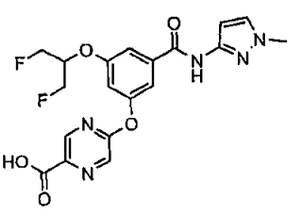
1H), 7.25 (s, 1H), 7.34 (s, 1H), 8.28 (d, 1H), 8.78 (d, 1H), 8.80 (s, 1H); *m/z* 473 $(M+H)^+$.

El siguiente compuesto se sintetizó en una forma análoga de ácido 5-[(3-[(1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico.

Ejemplo	Estructura	m/z	NMR
15a		437 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.38 (d, 6H), 2.40 (quintete, 2H), 3.83 (s, 3H), 4.28 (t, 2H), 4.62 (septete, 1H), 4.71 (t, 2H), 6.82 (s, 1H), 6.89 (t, 1H), 7.23 (s, 1H), 7.31 (m, 2H), 8.35 (s, 1H), 8.55 (s, 1H), 8.88 (s, 1H)

La preparación de 5-[(3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico se describe a continuación:

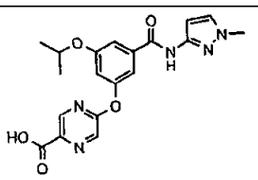
Ácido 5-[(3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico



Monohidrato de hidróxido de litio (77 mg, 1.82 mmol) en agua (2 mL) se agregó a metil 5-[(3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato (325 mg, 0.73 mmol) en THF (4 mL) y la mezcla se agitó a temperatura de la sala durante 20 horas. El THF se retiró *in vacuo* y el residuo acuoso se lavó con acetato de etilo para retirar las impurezas, luego se acidificó con 1M ácido cítrico. Se agregó acetato de etilo, y un sólido blanco se retiró por filtración y se secó *in vacuo* para producir el compuesto deseado como un sólido blanco

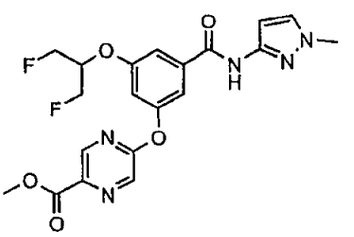
(0.28 g). ^{1}H NMR δ (d_6-DMSO): 3.79 (s, 3H), 4.77 (m, 4H), 5.12 (t, 1H), 6.59 (s, 1H), 7.22 (s, 1H), 7.50 (s, 1H), 7.62 (s, 2H), 8.69 (s, 1H), 8.80 (s, 1H), 10.90 (s, 1H), 13.50 (s, 1H), *m/z* 434 $(M+H)^+$.

Ácido 5-[(3-[(1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino] carbonil}fenil)oxi]pirazin-2-carboxílico, empleado en la preparación de Ejemplo 15a, se preparó en una forma análoga de metil 5-[(3-[(1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil) oxi]pirazin-2-carboxilato.

Estructura	m/z	NMR
	398 $(M+H)^+$	

La preparación de metil 5-[(3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato se describe a continuación:

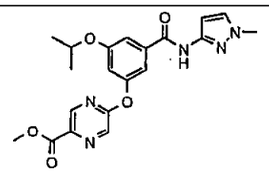
Metil 5-[(3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato



Una mezcla de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (250 mg, 0.8 mmol), metil 5-cloropirazin-2-carboxilato (208 mg, 1.20 mmol) y carbonato de potasio (222 mg, 1.61 mmol) en acetonitrilo (5 mL) se agitó en un 'Biotage initiator Microwave' a 120°C durante 3 horas. El disolvente se retiró *in vacuo*, y el residuo se

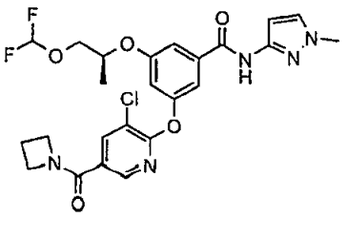
disolvió en acetato de etilo (50 mL) y agua (50 mL), la capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (0.325 g). ^{1}H NMR δ ($CDCl_3$): 3.71 (s, 3H), 3.96 (s, 3H), 4.56 (m, 2H), 4.68 (m, 3H), 6.73 (s, 1H), 6.95 (s, 1H), 7.22 (s, 1H), 7.27 (s, 1H), 7.36 (s, 1H), 8.46 (s, 1H), 8.67 (s, 1H), 8.67 (s, 1H); *m/z* 448 $(M+H)^+$.

El metil 5-[(3-[(1-metiletil)oxi]-5-{[(1-metil-1*H*-pirazol-3-il)amino] carbonil}fenil)oxi]pirazin-2-carboxilato, empleado en **Ejemplo 15a**, se preparó en una forma análoga de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*- pirazol-3-il)benzamida.

Estructura	m/z	NMR
	412 $(M+H)^+$	

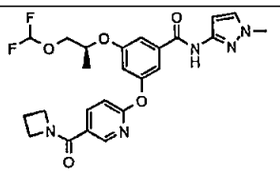
La preparación de 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-[(1-metiletil) oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describieron previamente.

Ejemplo 16: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



Una mezcla de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (110 mg, 0.32 mmol), 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (75 mg, 0.32 mmol) y carbonato de potasio (89 mg, 0.64 mmol) en acetonitrilo (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 3 horas. El disolvente se retiró *in vacuo*, y se agregó acetato de etilo (50 mL) al residuo, el cual se lavó con agua (20 mL), salmuera (50mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite amarillo. El residuo se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (92 mg). ^{1}H NMR δ ($CDCl_3$): 1.40 (d, 3H), 2.41 (quintete, 2H), 3.81 (s, 3H), 4.01 (mult, 2H), 4.26 (t, 2H), 4.38 (t, 2H), 4.67 (sextete, 1H), 6.29 (t, 1H), 6.82 (d, 1H), 6.96 (t, 1H), 7.27 (t, 1H), 7.31 (d, 1H), 7.38 (t, 1H), 8.18 (d, 1H), 8.26 (d, 1H), 8.77 (s, 1H), *m/z* 536 $(M+H)^+$.

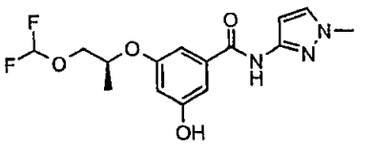
El siguiente compuesto se elaboró en una forma análoga de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 5-(azetidin-1-ilcarbonil)-2-cloropiridina.

Ejemplo	Estructura	m/z	NMR
16a		502 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.37 (d, 3H), 2.38 (quintete, 2H), 3.73 (s, 3H), 3.98 (m, 2H), 4.25 (t, 2H), 4.36 (t, 2H), 4.62 (sextete, 1H), 6.27 (t, 1H), 6.81 (d, 1H), 6.90 (t, 1H), 7.00 (d, 1H), 7.24 (t, 1H), 7.27 (m, 1H), 7.33 (m, 1H), 8.08 (m, 1H), 8.42 (d, 1H), 9.12 (s, 1H)

La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina y 5-(azetidin-1-ilcarbonil)-2-cloropiridina se describieron anteriormente.

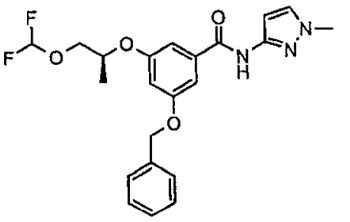
La preparación de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describe a continuación:

3-({(1*S*)-2-[(Difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



3-({(1*S*)-2-[(Difluorometil)oxi]-1-metiletil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (0.1 g, 0.23 mmol) se disolvió en etanol (3 mL) y THF (3 mL), y el matraz se vació y se purgó con argón (3 veces). Se agregó 10% paladio sobre carbón (0.01 g), y el matraz se volvió a vaciar y, finalmente, se purgó con gas hidrógeno. La mezcla de reacción se agitó a temperatura de la sala durante 20 horas hasta completarse. La mezcla de reacción se vació y se purgó con nitrógeno (3 veces). El catalizador se extrajo completamente por filtración a través de celita y el filtrado se concentró *in vacuo* para producir el compuesto deseado (70 mg). ^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 3.71 (s, 3H), 3.80-3.95 (m, 2H), 4.51 (sextete, 1H), 5.96-6.36 (t, 1H), 6.53 (s, 1H), 6.73 (s, 1H), 6.91 (s, 1H), 6.96 (s, 1H), 7.22 (s, 1H), 8.83 (s, 1H). *m/z* 342 $(M+H)^+$.

3-({(1*S*)-2-[(Difluorometil)oxi]-1-metiletil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida

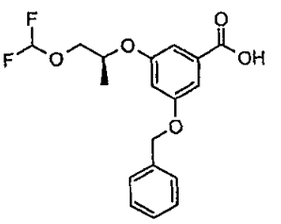


DIPEA (0.198 mL, 1.14 mmol) se agregó a una mezcla de ácido 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-[(fenilmetil)oxi]benzoico (0.1 g, 0.28 mmol), 3-amino-1-metil pirazol (39 mg, 0.4 mmol) y HATU (0.227 g, 0.6 mmol) en DMF (3 mL) y se agitó a temperatura de la sala durante 20 horas. Se agregó acetato de etilo (30 mL) y la mezcla se lavó con agua (30 mL), salmuera (30 mL), se secó ($MgSO_4$), se filtró y se redujo *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con

una gradiente de 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (0.1 g).

^{1}H. NMR δ ($CDCl_3$): 1.36 (d, 3H), 3.68 (s, 3H), 3.82-3.95 (m, 2H), 4.48 (sex, 1H), 5.00 (s, 2H), 6.19 (t, 1H), 6.63 (s, 1H), 6.73 (s, 1H), 6.93 (s, 1H), 7.03 (s, 1H), 7.28 (m, 1H), 7.35 (m, 5H), 8.59 (s, 1H). *m/z* 432 $(M+H)^+$.

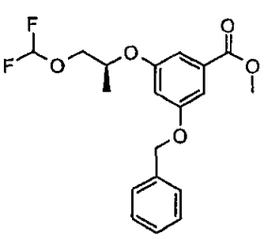
Ácido 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-[{fenilmetil)oxi] benzoico



Monohidrato de hidróxido de litio (19 mg, 0.45 mmol) en agua (2 mL) se agregó a metil 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-[(fenilmetil)oxi]benzoato (0.11 g, 0.3 mmol) en THF (4 mL), y la mezcla se agitó a temperatura de la sala durante 20 horas. El THF se retiró *in vacuo* y la capa acuosa se ajustó a pH3 con ácido cítrico, luego se extrajo en acetato de etilo (2 x 30 mL). Los orgánicos se lavaron con agua (30 mL), salmuera (30 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir el compuesto deseado (0.1 g).

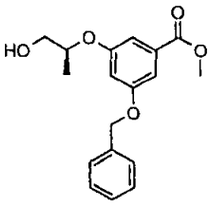
^{1}H NMR δ (d_6-DMSO): 1.27 (d, 3H), 4.00 (m, 2H), 4.75 (sextete, 1H), 5.15 (s, 2H), 6.72 (t, 1H), 7.08 (t, 1H), 7.16 (t, 1H), 7.41 (m, 5H), 12.95 (s, 1H). *m/z* 351 $(M+H)^+$.

Metil 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil)oxi)-5-[(fenilmetil)oxi] benzoato



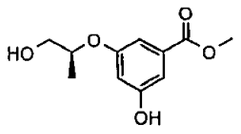
Ácido 2-(fluorosulfonil)difluoroacético (0.239 mL, 2.31 mmol) se agregó gota a gota, agitando simultáneamente, a una mezcla desgasificada de metil 3-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-5-[(fenilmetil)oxi]benzoato (0.73 g, 2.31 mmol) y yoduro de cobre (I) (88 mg, 0.46 mmol) en acetonitrilo (10 mL) a 45°C. La reacción se agitó a 45°C durante 24 horas. El disolvente se retiró *in vacuo* y se agregó acetato de etilo (30 mL). Los orgánicos se lavaron con agua (30 mL), salmuera (30 mL), se secaron ($MgSO_4$), se filtraron y el disolvente se retiró *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-30% acetato de etilo en isohexano, para producir el compuesto deseado (0.11 g).
^{1}H NMR δ ($CDCl_3$): 1.37 (d, 3H), 3.93 (s, 3H), 4.00 (m, 2H), 4.63 (sextete, 1H), 5.10 (s, 2H), 6.28 (t, 1H), 6.77 (t, 1H), 7.28 (t, 1H), 7.41 (m, 6H). *m/z* 367 $(MH\text{-}H)^+$.

Metil 3-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-5- [(fenilmetil) oxi]benzoato



Bromuro de bencilo (1.89 g, 7.20 mmol) se agregó a una mezcla de metil 3-hidroxi-5-[(1*S*)-2-hidroxi-1-metiletoxi]benzoato (1.55 g, 6.86 mmol) y carbonato de potasio (1.89 g, 0.014 mol) en DMF (16 mL), y la reacción se agitó a temperatura de la sala durante 20 horas. Se agregó acetato de etilo (40 mL), y la mezcla se lavó con agua (40 mL), solución de bicarbonato de sodio saturado (40 mL), salmuera (40 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite rojo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (1.7 g).
^{1}H NMR δ ($CDCl_3$): 1.30 (d, 3H), 1.95 (m, 1H), 3.76 (m, 2H), 3.92 (s, 3H), 4.53 (m, 1H), 5.11 (s, 2H), 6.78 (t, 1H), 7.25 (m, 1H), 7.32 (m, 1H), 7.45 (m, 5H). *m/z* 317 $(M+H)^+$.

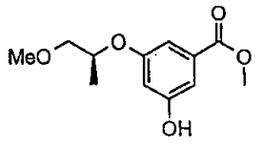
Metil 3-hidroxi-5 –[(1*S*)-2-hidroxi-1-metiletoxi]benzoato



Yoduro de trimetilsililo (115 mL, 0.79mol) se agregó a una solución de metil 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]benzoato (38.01 g, 0.158mol) en acetonitrilo (500 mL) y se agitó durante 24 horas. Se agregó metanol (300 mL) y la reacción se agitó durante 10 minutos. Se agregó a la mezcla 10% p/v de pentahidrato de tiosulfato de sodio acuoso (100 mL) y se agitó durante 20 minutos. La mezcla de reacción se neutralizó con solución de bicarbonato de sodio acuoso saturado, los disolventes orgánicos se retiraron *in vacuo*, y el producto se extrajo en acetato de etilo (4 x 100 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y los disolventes se retiraron *in vacuo*. El material crudo se cristalizó de acetato de etilo para producir el compuesto del título (16.80 g).

^{1}H NMR δ (d_6-DMSO): 1.18 (d, 3H), 3.40-3.55 (m, 2H), 3.80 (s, 3H), 4.35 (sex, 1H), 4.80 (t, 1H), 6.57 (m, 1H), 6.90 (m, 2H), 9.75 (s, 1H). *m/z* 304 $(M+H)^+$

Metil 3-Hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]benzoato

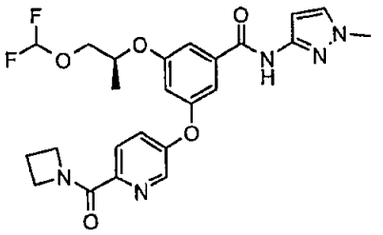


Metil 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoato (50.0 g, 0.152 mmol) se disolvió en una mezcla de THF:etanol (600 mL) y el matraz se vació y se purgó con nitrógeno (3 veces). 10% Paladio sobre carbón (5.0 g) se agregó y el matraz se volvió a vaciar y, finalmente, se purgó con gas hidrógeno. La mezcla de reacción se agitó a temperatura ambiente durante 20 horas hasta completarse. La mezcla de reacción se vació y se purgó con nitrógeno (3 veces). El catalizador se extrajo completamente por filtración, y el filtrado se concentró *in vacuo* para producir el compuesto deseado (36.7 g).

^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 3.25 (s, 3H), 3.44 (m, 2H), 3.82 (s, 3H), 4.55 (m, 1H), 6.6 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 9.8 (s, 1H).

La preparación de metil 3-[(1S)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil] oxi}benzoato se describió previamente.

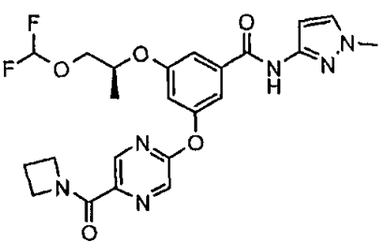
Ejemplo 17: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



Una mezcla de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (220 mg, 0.64 mmol), 2-(azetidin-1-ilcarbonil)-5- bromopiridina (171 mg, 0.71 mmol), carbonato de cesio (419 mg, 1.29 mmol) y bromotris(trifenilfosfina)cobre(I) (300 mg, 0.32 mmol) en DMA (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 4 horas. La mezcla de reacción se agregó a acetato de etilo (50 mL) y agua (50 mL), la capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite marrón. El residuo se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto deseado (102 mg). ^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.28 (quintete, 2H), 3.68 (s, 3H), 3.90 (mult, 2H), 4.17 (t, 2H), 4.54 (sextete, 1H), 4.63 (t, 2H), 6.19 (t, 1H), 6.71 (t, 1H), 6.73 (s, 1H), 7.06 (s, 1H), 7.22 (mult, 2H), 7.30 (multiplete, 1H), 8.04 (d, 1H), 8.24 (d, 1H), 8.84 (s, 1H); *m/z* 502 $(M+H)^+$.

La preparación de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describieron anteriormente.

Ejemplo 18: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi)-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il) benzamida

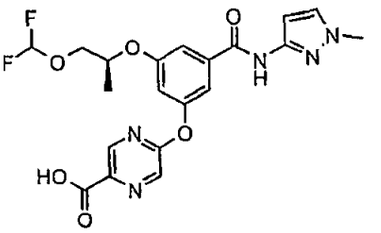


DIPEA (0.41 mL, 2.33 mmol) se agregó a una mezcla de ácido 5-[(3-({(1S)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-{[(1-metil-1*H*-pirazol-3-il) amino]carbonil}fenil)oxi]pirazin-2-carboxílico (0.27 g, 0.58 mmol), clorhidrato de azetidina (109 mg, 1.17 mmol) y HATU (466 mg, 1.22 mmol) en DMF (5 mL) y se agitó a temperatura de la sala durante 24 horas. Se agregó acetato de etilo (40 mL), y los orgánicos se lavaron con agua (2 x 30 mL), salmuera (30 mL), se secaron ($MgSO_4$), se filtraron y se concentraron *in vacuo* para producir un aceite amarillo. El residuo se cromatografió en sílice, eluyendo con 0-5% metanol en acetato de etilo, para producir el compuesto deseado (124 mg).

^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.30 (quintete, 2H), 3.65 (s, 3H), 3.90 (m, 2H), 4.18 (t, 2H), 4.53 (sextete, 1H), 4.61 (t, 2H), 6.19 (t, 1H), 6.73 (d, 1H), 6.84 (t, 1H), 7.18 (m, 2H), 7.28 (s, 1H), 8.25 (s, 1H), 8.76 (s, 1H), 9.14 (s, 1H); *m/z* 503 $(M+H)^+$.

La preparación de 5-[(3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico se describe a continuación:

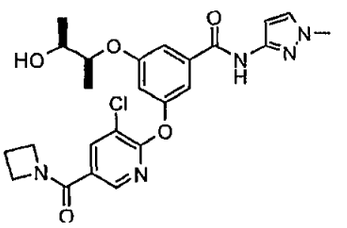
Ácido 5-[(3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico



Una mezcla de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (220 mg, 0.64 mmol), metil 5-cloropirazin-2-carboxilato (112 mg, 0.64 mmol) y carbonato de potasio (178 mg, 1.29 mmol) en acetonitrilo (5 mL) se agitó en un 'Biotage initiator Microwave' a 160°C durante 4 horas. El disolvente se retiró *in vacuo*, y se agregó agua (20 mL). La mezcla se ajustó a pH3 con 1M ácido cítrico y se extrajo en acetato de etilo (2 x 50 mL). Los orgánicos combinados se lavaron con agua (20 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir un aceite amarillo (0.19 g), el cual pareció ser una mezcla del ácido y éster metílico. Monohidrato de hidróxido de litio (26 mg, 0.60 mmol) en agua (3 mL) se agregó a la mezcla de ácido y éster (0.19 g, 0.4 mmol) en THF (6 mL), y la mezcla se agitó a temperatura de la sala durante 72 horas. Los orgánicos se retiraron *in vacuo* y el residuo se ajustó a pH3 con 1M ácido cítrico, se extrajo dos veces en acetato de etilo, y los orgánicos combinados se lavaron con agua (30 mL), salmuera (30 mL), se secaron ($MgSO_4$), se filtraron y el disolvente se retiró *in vacuo* para producir el compuesto deseado como un sólido amarillo (0.17 g). *m/z* 464 $(M+H)^+$.

La preparación de 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describió anteriormente.

Ejemplo 19: 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida y 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*,2*S*)-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida (1:1)



Una solución de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (95 mg, 0.44 mmol), una mezcla de 3-hidroxi-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1:1) (129 mg, 0.42 mmol) y carbonato de potasio (146 mg, 1.05 mmol) en acetonitrilo (3 mL) se calentó en un reactor microondas a 160°C durante 5 horas. El acetonitrilo se retiró *in vacuo* y el residuo se disolvió en acetato de etilo (25 mL). La solución orgánica se lavó con agua (25 mL), salmuera (25 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en alúmina, eluyendo con una gradiente de 0-5% metanol en acetato de etilo, para proporcionar el producto requerido (56 mg).

^{1}H NMR δ ($CDCl_3$): 1.18 (m, 6H), 2.32 (m, 3H), 3.66 (s, 3H), 3.79 (quintete, 1H), 4.15 (m, 3H), 4.28 (t, 2H), 6.72 (d, 1H), 6.85 (t, 1H), 7.17 (s, 1H), 7.19 (s, 1H), 7.29 (s, 1H), 8.08 (m, 1H), 8.15 (m, 1H), 9.10 (s, 1H); *m/z* 501 $(MH\text{-}H)^+$.

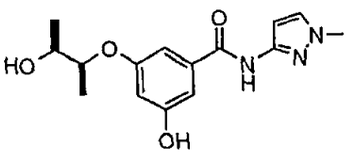
Esta mezcla de diastereómeros se separó mediante HPLC quiral preparatoria en una columna Chiralpak IA (250mm x 20mm) No. EG014, eluyendo con una mezcla de isohexano / acetato de etilo / ácido acético / trietilamina (40 / 60 / 0.2 / 0.1) para producir el primer isómero eluido (43 mg), **Ejemplo 19a**, y el segundo isómero eluido (40 mg), **Ejemplo 19b**.

La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describió anteriormente.

La preparación de 3-hidroxi-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil] oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1:1) se describe a continuación:

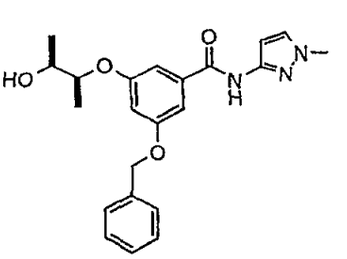
424

3-Hidroxi-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1:1)



Una solución de una mezcla de 3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida y 3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (1 : 1) (1.26 g, 3.19 mmol) y 10% en peso de paladio sobre carbón (0.13 g) en etanol (50 mL) se dejó agitando a temperatura de la sala bajo una atmósfera de hidrógeno durante 16 horas. La solución se filtró a través de Celite® y se lavó concienzudamente con metanol (100 mL). La solución se concentró *in vacuo* para producir el compuesto deseado (1.03g). ^{1}H NMR δ (d_6-DMSO): 1.09 (d, 3H), 1.17 (d, 3H), 3.76 (m, 1H), 3.78 (s, 3H), 4.34 (quintete, 1H), 6.48 (t, 1H), 6.56 (d, 1H), 6.93 (t, 1H), 7.05 (t, 1H), 7.60 (d, 1H), 9.66 (s, 1H), 10.67 (s, 1H); *m/z* 306 $(M+H)^+$.

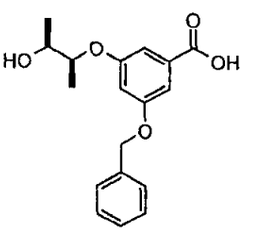
3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida y 3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi] benzamida (1:1)



Una solución de una mezcla de ácido 3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoico y ácido 3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoico (1:1) (2.50 g, 7.92 mmol), 1-metil-1*H*-pirazol-3-amina (1.54 g, 15.8 mmol), HATU (3.92 g, 10.3 mmol)

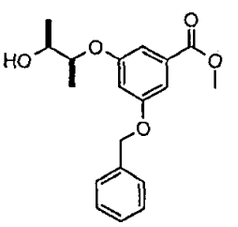
y DIPEA (2.76 mL, 15.8 mmol) en DMF (15 mL) se agitó a temperatura de la sala y bajo atmósfera ambiente durante 16 horas. Se agregó agua (150 mL) y la solución se extrajo con acetato de etilo (250 mL). La capa de acetato de etilo se lavó con salmuera y se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en hexano, para producir el producto deseado (1.26 g). ^{1}H NMR δ ($CDCl_3$): 1.17 (s, 3H), 1.18 (s, 3H), 2.44 (d, 1H), 3.70 (s, 3H), 3.77 (m, 1H), 4.10 (quintete, 1H), 4.99 (s, 2H), 6.64 (t, 1H), 6.75 (d, 1H), 6.96 (t, 1H), 7.03 (t, 1H), 7.22 (d, 1H), 7.31 (m, 5H), 8.68 (s, 1H); *m/z* 396 $(M+H)^+$.

Ácido 3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoico y ácido 3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil)oxi] benzoico (1:1)



A una solución de una mezcla de metil 3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoato y metil 3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil)oxi]benzoato (1:1) (2.52 g, 7.63 mmol) en THF (40 mL) se agregó una solución de monohidrato de hidróxido de litio (0.80 g, 19.07 mmol) en agua (10 mL). La mezcla se dejó agitando a temperatura de la sala durante 16 horas. El THF se retiró *in vacuo*, y la solución resultante se repartió en porciones entre agua (100 mL) y acetato de etilo (250 mL). La capa de acetato de etilo se lavó con salmuera (50 mL) y se secó ($MgSO_4$). La capa acuosa se ajustó entonces a pH 7 mediante la adición de 1M ácido clorhídrico y se extrajo con acetato de etilo (75 mL). La capa de acetato de etilo se lavó con salmuera y se secó ($MgSO_4$). Las capas de acetato de etilo se combinaron y se evaporaron para proporcionar el producto requerido (2.50 g). ^{1}H NMR δ ($CDCl_3$): 1.18 (s, 3H), 1.20 (s, 3H), 3.80 (quintete, 1H), 4.14 (quintete, 1H), 5.01 (s, 2H), 6.72 (t, 1H), 7.21 (m, 1H), 7.32 (m, 6H).

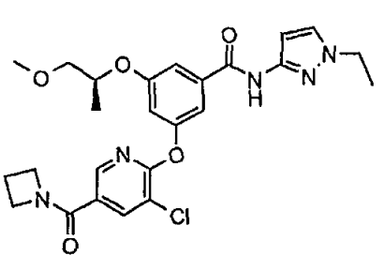
Metil 3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-[(fenilmetil) oxi]benzoato y metil 3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5- [(fenilmetil)oxi] benzoato (1:1)



Una solución de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (3.00 g, 11.61 mmol), (2*R*,3*S*)-2,3-dimetiloxirano (3.04 mL, 34.8 mmol), y carbonato de potasio (4.02 g, 29.0 mmol) en acetonitrilo (60 mL) se calentó en un reactor microondas a 150°C durante 3 horas. El acetonitrilo se retiró *in vacuo* y el aceite residual se disolvió en acetato de etilo (50 mL), se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$) y se evaporó a un aceite residual. El residuo se cromatografió en sílice, eluyendo con acetato de etilo, para producir el compuesto deseado (2.52 g). ^{1}H NMR δ ($CDCl_3$): 1.17 (d, 6H), 3.82 (s, 3H), 4.04 (q, 2H), 4.99 (s, 2H), 6.67 (t, 1H), 7.14 (s, 1H), 7.30 (m, 6H); *m/z* 330 $(M-H)^-$.

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente.

Ejemplo 20: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-1-il]oxi}-*N*-(1-etil-1*H*-pirazol-3-il)-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida



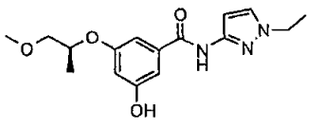
Una solución de *N*-(1-etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida (128 mg, 0. 4 mmol) y la 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (111 mg, 0.48 mmol) en acetonitrilo (2 mL),

que contenía carbonato de potasio (111 mg, 0.8 mmol), se calentó en un reactor microondas a 160°C durante 6 horas. La mezcla de reacción se filtró y el filtrado se evaporó a sequedad bajo presión reducida y se purificó por cromatografía en sílice, eluyendo con 50-100% acetato de etilo en hexano para proporcionar el producto requerido como una espuma blanca (176 mg).

^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 1.41 (t, 3H), 2.32 (quintete, 2H), 3.35 (s, 3H), 3.49 (m, 2H), 4.02 (q, 2H), 4.17 (t, 2H), 4.30 (t, 2H), 4.56 (q, 1H), 6.76 (d, 1H), 6.88 (t, 1H), 7.18 (s, 1H), 7.28 (d, 1H), 7.32 (t, 1H), 8.09 (d, 1H), 8.18 (d, 1H), 8.65 (s, 1H); *m/z* 514 $(M+H)^+$.

La preparación de N-(1-etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida se describe a continuación:

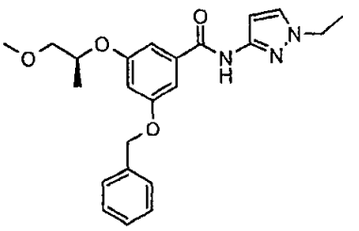
N-(1-Etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi} benzamida



10% Paladio sobre carbón (1.9 g, 50% húmedo) se agregó bajo argón a *N*-(1-etil-1*H*-pirazol-3-il)-3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil)oxi]benzamida (19.1 g, 46.7 mmol) en THF seco (100 mL) y etanol (100 mL). La mezcla de reacción se desgasificó, se puso bajo un balón de hidrógeno y se agitó durante 16 horas. La mezcla se filtró a través de tierra de diatomeas y el filtrado se evaporó para producir un aceite marrón. El residuo se purificó por cromatografía en columna en sílice, eluyendo con 40-65% acetato de etilo en hexanos, para producir el producto deseado como un aceite claro, el cual se cristalizó al reposar (11.35 g).

^{1}H NMR δ ($CDCl_3$): 1.21 (d, 6H), 1.38 (t, 3H), 3.32 (s, 3H), 3.39 - 3.51 (m, 3H), 3.98 (q, 2H), 4.44 - 4.51 (m, 1H), 6.54 (s, 1H), 6.72 (d, 1H), 6.92 (s, 2H), 7.26 (d, 1H), 8.18 (s, 1H), 8.85 (s, 1H); *m/z* 320 $(M+H)^+$ 318 $(M-H)^-$.

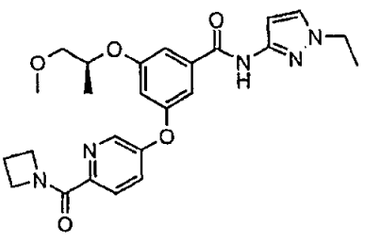
N-(1-Etil-1*H*-pirazol-3-il)-3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil)oxi]benzamida



HATU (23.5 g, 61.83 mmol) se agregó a ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico (16.28 g, 51.53 mmol), seguido por la adición de DMF (140 mL) y se enfrió a 0°C. Se agregó 1-etil-1*H*-pirazol-3-amina (6.86 g, 61.8 mmol), seguida por DIPEA (21.3 mL) y la reacción se agitó bajo argón, a 0°C, durante 3 horas. El volumen de disolvente se redujo y el residuo se disolvió en acetato de etilo (500 mL), se lavó con ácido cítrico (200 mL), solución de bicarbonato de sodio (150 mL) y solución de salmuera saturada (2 x 150 mL). La capa orgánica se separó y se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía en columna en sílice, eluyendo con 10-50% acetato de etilo en hexanos, produjo el compuesto del título como un aceite amarillo pálido (19.1 g).
^{1}H NMR δ ($CDCl_3$): 1.23 (d, 3H), 1.38 (t, 3H), 3.33 (s, 3H), 3.42 (dd, 1H), 3.50 (dd, 1H), 3.97 (q, 2H), 4.49 (sextete, 1H), 4.99 (s, 2H), 6.66 (t, 1H), 6.75 (d, 1H), 6.98 (s, 1H), 7.02 (s, 1H), 7.26 (d, 1H), 7.28 - 7.37 (m, 5H), 8.58 (s, 1H); *m/z* 410 $(M+H)^+$

La preparación de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico se describió anteriormente.
La preparación de 1-etil-1*H*-pirazol-3-amina se describe en la literatura [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 11, **1975**, 212].

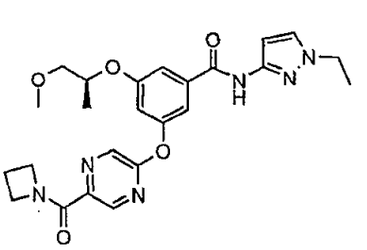
Ejemplo 21: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(1-etil-1*H*-pirazol-3-il)-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida



Una mezcla de *N*-(1-etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida (0.128g, 0.4 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (116 mg, 0..48 mmol), carbonato de cesio (392 mg, 1.2 mmol) y bromotris(trifenilfosfina)cobre(I) (38 mg, 0.04 mmol) en DMA (5 mL) se agitó en un reactor microondas a 160°C durante 4 horas. El producto se disolvió en acetato de etilo (20 mL) y agua (15 mL) y las capas se separaron. La capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró y el disolvente se retiró *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con una gradiente de 70-100% acetato de etilo en hexano para producir el material deseado como una espuma clara (76 mg). ^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 1.40 (t, 3H), 2.29 (quintete, 2H), 3.34 (s, 3H), 3.42 - 3.53 (m, 2H), 4.01 (q, 2H), 4.18 (t, 2H), 4.54 (q, 1H), 4.64 (t, 2H), 6.74 (t, 2H), 7.04 (s, 1H), 7.22 (s, 1H), 7.27 (d, 1H), 7.30 (d, 1H), 8.04 (d, 1H), 8.25 (d, 1H), 8.47 (s, 1H); *m/z* 480 $(M+H)^+$.

La preparación de *N*-(1-etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describió anteriormente.

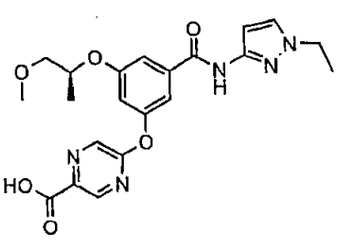
Ejemplo 22: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-*N*-(1-etil-1*H*-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida



HATU (304 mg, 0.80 mmol) se agregó a ácido 5-[(3-{[(1-etil-1*H*-pirazol-3-il)amino]carbonil}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)oxi]pirazin-2-carboxílico (0.4 mmol) y clorhidrato de azetidina (75 mg, 0.89 mmol) en DMF (5 mL), seguido por la adición de DIPEA (0.278 mL, 1.6 mmol), y la reacción se agitó durante 16 horas. La mezcla de reacción se agregó a acetato de etilo (20 mL), la solución orgánica se lavó con agua (10 mL), 2N ácido cítrico (10 mL), bicarbonato de sodio acuoso saturado (10 mL) y salmuera (10 mL), luego se secó ($MgSO_4$), se filtró y se evaporó bajo presión reducida a una goma. El residuo se purificó por cromatografía en sílice, eluyendo con 70-100% acetato de etilo en hexano, para producir el compuesto deseado como una espuma blanca (98 mg). ^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 1.40 (t, 3H), 2.31 (quintete, 2H), 3.34 (s, 3H), 3.43 - 3.54 (m, 2H), 4.01 (q, 2H), 4.19 (t, 2H), 4.54 (q, 1H), 4.62 (t, 2H), 6.73 (d, 1H), 6.87 (t, 1H), 7.18 (t, 1H), 7.27 (d, 1H), 7.30 (t, 1H), 8.26 (d, 1H), 8.49 (s, 1H), 8.78 (d, 1H); *m/z* 481 $(M+H)^+$.

La preparación de ácido 5-[(3-{[(1-etil-1*H*-pirazol-3-il)amino]carbonil}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)oxi]pirazin-2-carboxílico se describe a continuación:

Ácido 5-[(3-{[(1-etil-1*H*-pirazol-3-il)amino]carbonil}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)oxi]pirazin-2-carboxílico

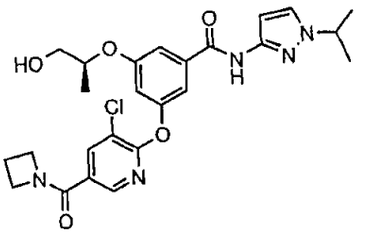


Una solución de *N*-(1-etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida (128 mg, 0.4 mmol) y el metil-5-cloropirazin-2-carboxilato (83 mg, 0.48 mmol) en acetonitrilo (2 mL), que contenía carbonato de potasio (111 mg, 0.8 mmol), se calentó en un reactor microondas a 160°C durante 6 horas. La mezcla de reacción se disolvió en

agua (10 mL), se acidificó con 2N ácido cítrico y se extrajo con acetato de etilo (5 x 20 mL). La fase orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a sequedad bajo presión reducida para producir el material deseado como un sólido amarillo (164 mg), el cual se utilizó sin purificación posterior en el siguiente paso, *m/z* 442 $(M+H)^+$.

La preparación de N-(1-etil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1,S)-1-metil-2-(metiloxi)etil]oxi}benzamida se describió anteriormente.

Ejemplo 23: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il] benzamida

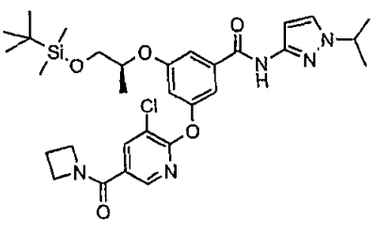


3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1S)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il]benzamida (142 mg, 0.23 mmol) en metanol (2 mL) se agitó con 3.5M ácido clorhídrico (0.2 mL, 0.68 mmol) durante 1 hora. La solución se neutralizó con solución de bicarbonato de sodio saturado y el disolvente orgánico se retiró bajo presión reducida. El residuo se extrajo con acetato de etilo (3 x 10 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró bajo presión reducida. El residuo se purificó por cromatografía en sílice, eluyendo con 75-100% acetato de etilo en hexano, para proporcionar el producto requerido como una espuma blanca (99 mg).

^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 1.41 (d, 6H), 2.32 (quintete, 2H), 3.67 - 3.71 (m, 2H), 4.17 (t, 2H), 4.26 - 4.35 (m, 3H), 4.52 (q, 1H), 6.73 (s, 1H), 6.87 (s, 1H), 7.19 (s, 1H), 7.30 (s, 1H), 7.32 (s, 1H), 8.10 (s, 1H), 8.18 (s, 1H), 8.56 (s, 1H); *m/z* 514 $(M+H)^+$.

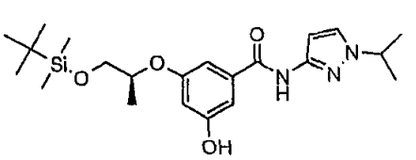
La preparación de 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il]benzamida se describe a continuación:

3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-[1-(1-metiletil-1*H*-pirazol-3-ilbenzamida



Una solución de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il]benzamida (103 mg, 0.24 mmol) y 5- (azetidin-1-ilcarbonil)-2,3-dicloropiridina (66 mg, 0.29 mmol) en acetonitrilo (2 mL), que contenía carbonato de potasio (66 mg, 0.48 mmol), se calentó en un reactor microondas a 160°C durante 6 horas. La mezcla de reacción se filtró y el filtrado se evaporó a sequedad bajo presión reducida y se purificó por cromatografía en sílice, eluyendo con 50-100% acetato de etilo en hexano, para proporcionar el producto requerido como una espuma blanca (142 mg). *m/z* 628 $(M+H)^+$.

3-[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il]benzamida

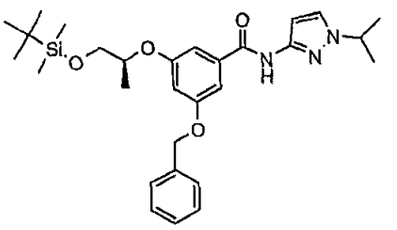


Una solución de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il]-5-[(fenilmetil) oxi]benzamida (1.97 g, 3.77 mmol) y THF (70 mL) se vació y purgó con argón (x3). Se agregó paladio sobre carbón (10% w/w, 400 mg) y la mezcla de reacción se vació y, finalmente, purgó con gas hidrógeno. La mezcla de

reacción se dejó agitando a temperatura ambiente bajo hidrógeno durante 16 horas. El paladio sobre carbón se extrajo completamente por filtración y se concentró *in vacuo* para producir el producto como un aceite incoloro (1.58 g, 97%).

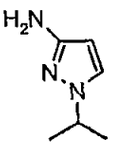
^{1}H NMR δ ($CDCl_3$): 0.02 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.27 (d, 3H), 1.53 (s, 3H), 1.55 (s, 3H), 3.63 (dd, 1H), 3.77 (dd, 1H), 4.41 (m, 1H), 6.60 (s, 1H), 6.81 (s, 1H), 7.00 (s, 1H), 7.07 (s, 1H), 7.38 (s, 1H), 8.78 (br. s, 1H); *m/z* 434 $(M+H)^+$, 432 $(M-H)^-$.

3[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-[1-(1-metiletil)-1*H*-pirazol-3-il]-5-[(fenilmetil)oxi]benzamida



DIPEA (3.11 mL, 18.03 mmol) se agregó a una solución de ácido 3-[((1S)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-[(fenilmetil) oxi]benzoico (3.00 g, 7.21 mmol), HATU (3.12 g, 8.21 mmol) y 1-(1-metiletil)-1*H*-pirazol-3-amina (1.13 g, 9.01 mmol) en DMF (10 mL). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. El DMF se retiró *in vacuo*. El disolvente se evaporó y el residuo se disolvió en 5% p/v ácido cítrico (50 mL) y acetato de etilo (30 mL) y éter dietílico (30 mL), y la capa orgánica se lavó posteriormente con solución de bicarbonato de sodio acuoso saturado (30 mL) y salmuera (30 mL). La capa orgánica se separó, luego se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía en columna, eluyendo con 1:4 a 1:3 acetato de etilo :hexanos, produjo el compuesto del título como un aceite incoloro (2.40 g, 65%). ^{1}H NMR δ ($CDCl_3$): 0.01 (s, 3H), 0.03 (s, 3H), 0.86 (s, 9H), 1.24 (d, 3H), 1.49 (s, 3H), 1.51 (s, 3H), 3.64 (dd, 1H), 3.78 (dd, 1H), 4.39 (m, 1H), 4.46 (m, 1H), 5.09 (s, 2H), 6.70 (s, 1H), 6.78 (s, 1H), 7.02 (s, 1H), 7.08 (s, 1H), 7.35 (m, 6H), 8.32 (br. s, 1H); *m/z* 524 $(M+H)^+$, 522 $(M-H)^-$.

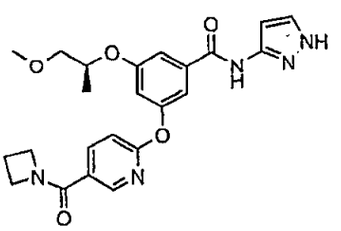
1-(1-Metiletil)-1*H*-pirazol-3-amina



2-Cloroacrilonitrilo (3.41 mL, 42.59 mmol) se agregó a temperatura de la sala a una solución en agitación de clorhidrato de *N*-isopropilhidrazina (4.71 g, 42.6 mmol), carbonato de potasio (11.8 g, 85.2 mmol) en agua (50 mL). La reacción se calentó a 45°C durante 4 horas antes de volver a enfriar a temperatura de la sala. La capa acuosa se extrajo entonces con acetato de etilo (5 x 30 mL) y las capas orgánicas combinadas se secaron ($MgSO_4$), se trataron con carbón vegetal activado, se filtraron y se evaporaron. El residuo se purificó por cromatografía, eluyendo con 67%-100% acetato de etilo en hexanos, para producir el compuesto del título (3.08 g, 58%) como una 6:1 mezcla de producto auténtico a producto regioisomérico como un aceite. El material se utilizó sin purificación posterior. ^{1}H NMR δ ($CDCl_3$): 1.42 (m, 6H), 3.58 (br. s, 2H), 4.25 (septete, 1H), 5.58 (d, 1H), 7.15 (d, 1H).

La preparación de ácido 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico se describió anteriormente.

Ejemplo 24: 3-{[5-(Azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-1*H*-pirazol-3-ilbenzamida

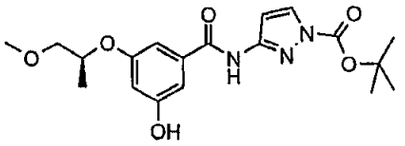


Una solución de 1,1-dimetiletil 3-{[(3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)carbonil]amino}-1*H*-pirazol-1-carboxilato (157 mg, 0.4 mmol) y 5-(azetidin-1-ilcarbonil)-2-cloropiridina (95 mg, 0.48 mmol) en acetonitrilo (2 mL), que contenía carbonato de potasio (111 mg, 0.8

mmol), se calentó en un reactor microondas a 160°C durante 6 horas. La mezcla de reacción se filtró y el filtrado se evaporó a sequedad bajo presión reducida y se purificó por cromatografía en sílice, eluyendo con 50-100% acetato de etilo en hexano para proporcionar un producto, el cual se purificó aún más por cromatografía en sílice, eluyendo con 0-8% metanol en acetato de etilo, para proporcionar el producto requerido como una espuma blanca (21 mg). ^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.30 (quintete, 2H), 3.33 (s, 3H), 3.42 - 3.54 (m, 2H), 4.12 - 4.29 (m, 4H), 4.54 (q, 1H), 6.77 (s, 1H), 6.81 (t, 1H), 6.97 (d, 1H), 7.20 (s, 1H), 7.27 (s, 1H), 7.33 (d, 1H), 8.01 (d, 2H), 8.28 (d, 1H), 10.27 (s, 1H); *m/z* 452 $(M+H)^+$.

La preparación de 1,1-dimetiletil 3-{[(3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)carbonil]amino}-1*H*-pirazol-1-carboxilato se describe a continuación:

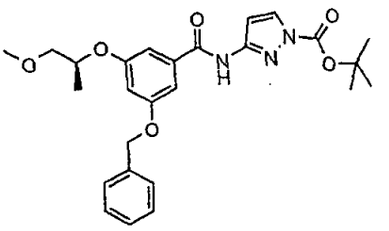
1,1-Dimetiletil 3-{[(3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil) carbonil]amino}-1*H*-pirazol-1-carboxilato



Una solución de 1,1-dimetiletil 3-[({3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil)oxi]fenil}carbonil)amino]-1*H*-pirazol-1-carboxilato (23 g, 47.8 mmol) en THF (140 mL) y etanol (140 mL) se vació y se purgó con nitrógeno (x3). Se agregó 10% paladio sobre carbón (2.3 g; 10% p/p) y mezcla de reacción se vació y, finalmente, purgó con gas hidrógeno. La mezcla de reacción se dejó agitando a temperatura de la sala bajo un balón de hidrógeno durante 16 horas. El paladio en carbón se filtró a través de tierra de diatomeas y el filtrado se concentró *in vacuo* para producir una espuma blanca (18 g, 97%). ^{1}H NMR δ (d_6-DMSO): 1.2 (d, 3H), 1.55 (s, 9H), 3.25 (s, 3H pico oscurecido por la presencia de agua), 3.4- 3.5 (m, 2H),

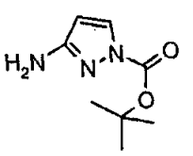
4.7 (m, 1H), 6.5 (s, 1H), 6.95 (d, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 8.2 (d, 1H), 9.65 (s, 1H), 11.2 (s, br, 1H); *m/z* 392 $(M+H)^+$.

1,1-Dimetiletil-3-[({3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil) oxi]fenil}carbonil)amino]-1*H*-pirazol-1-carboxilato



DIPEA (28.5 mL, 164 mmol) se agregó a una suspensión de ácido 3-[(1S)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico (20.7 g, 65.6 mmol), HATU (31.2 g, 82.0 mmol) y 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato (15.0 g, 82.0 mmol) en DMF (30 mL), y la mezcla de reacción se agitó durante 16 horas a temperatura de la sala. Se agregó agua (250 mL) y la mezcla de reacción se extrajo con éter dietílico (3 x 150 mL). La capa orgánica se lavó con solución de salmuera saturada y se secó ($MgSO_4$). El filtrado se concentró *in vacuo* y el residuo se cristalizó luego de reposar. Los cristales se lavaron con isohexano para producir el material deseado como cristales amarillos (23.4 g; 73%). *m/z* 482 $(M+H)^+$.

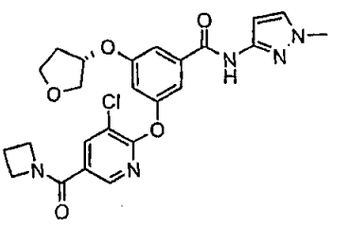
1,1-Dimetiletil 3-amino-1*H*-pirazol-1-carboxilato



1*H*-Pirazol-3-amina (428 mg, 5.15 mmol) se disolvió en DMF (5 mL) a 0°C y se trató con hidruro de sodio (206 mg, 5.15 mmol), seguido por agitación durante 30 minutos más. Luego se agregó lentamente di-*terc*-butil dicarbonato calentado (1.12 g, 5.15 mmol) mediante una jeringa durante 5 minutos, y la reacción se dejó calentar a temperatura de la sala y se agitó durante 2 horas más. La reacción se tomó en bicarbonato de sodio acuoso saturado (50 mL) y acetato de etilo (100 mL). La capa orgánica se separó,

luego se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía en columna (eluyendo con 1:1 acetato de etilo:hexanos a acetato de etilo puro) produjo el compuesto del título (117 mg) como un sólido blanco. ^{1}H NMR δ ($CDCl_3$): 1.62 (s, 9H), 4.00 (br. s, 2H), 5.81 (d, 1H), 7.82 (d, 1H). Se preparó asimismo 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato haciendo reaccionar una solución de 1*H*-pirazol-3-amina en THF (1 g en aproximadamente 15.6 mL) con NaHMDS (2M en THF, 1.05 equivalentes), luego agregando una solución de di-*terc*-butil dicarbonato (1 equivalente) en THF (aproximadamente 1g de dicarbonato en 1.9 mL) y agitando a temperatura de la sala. El material resultante se cristalizó de una mezcla de acetato de etilo e isohexano. La preparación de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico se describió anteriormente.

Ejemplo 25: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-1-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzamida

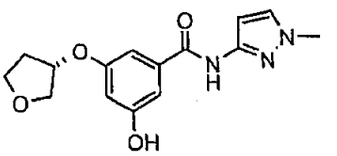


Una mezcla de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida (80 mg, 0.26 mmol), 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (61 mg, 0.26 mmol) y carbonato de cesio (172 mg, 0.53 mmol) en acetonitrilo (3 mL) se agitó en un microondas Smith Creator a 160°C durante 3 horas. El disolvente se retiró *in vacuo* y se agregó acetato de etilo (50 mL) al residuo. La fase orgánica se lavó con agua (20 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en DCM, para producir el compuesto del título como una espuma amarilla (52 mg). ^{1}HNMR δ ($CDCl_3$): 2.16 - 2.24 (2H, m), 2.34 - 2.44 (4H, m), 3.78 (3H, s), 3.89 - 4.01 (4H, m), 4.24 (2H, t), 4.37 (2H, t), 4.99 (1H, s), 6.80 (1H, s),

6.89 (1H, s), 7.23 (1H, s), 7.30 (2H, d), 8.16 (1H, s), 8.24 (1H, s), 8.73 (1H, s); *m/z* 498 $(M+H)^+$.

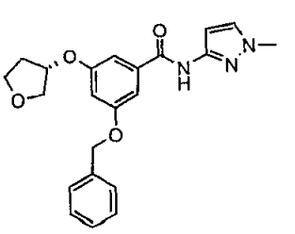
La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describió anteriormente. La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida se describe a continuación:

3-Hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzamida



N-(1-Metil-1*H*-pirazol-3-il)-3-[(fenilmetil)oxi]-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida (453 mg, 1.15 mmol) se disolvió en etanol (5 mL) y se agregó formiato de amonio (182 mg, 2.88 mmol) en una porción. La reacción se cubrió con argón y se agregó 10% paladio sobre carbón activado (30 mg). Esta mezcla se calentó a 140°C durante 10 minutos en un microondas Smith Creator. El catalizador se extrajo completamente por filtración y los volátiles se retiraron *in vacuo* para proporcionar el producto del título como un sólido blanco (339 mg). ^{1}H NMR δ ($CDCl_3$): 2.06 - 2.14 (1H, m), 2.15 - 2.22 (1H, m), 3.72 - 3.73 (3H, s), 3.84 - 3.89 (1H, m), 3.92 - 3.98 (3H, m), 4.88 (1H, m), 6.53 (1H, t), 6.78 (1H, d), 6.89 (1H, s), 6.95 (1H, s), 7.28 (1H, d), 9.27 (1H, s); *m/z* 304 $(M+H)^+$.

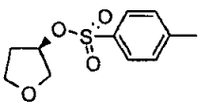
N-(1-Metil-1*H*-pirazol-3-il)-3-[(fenilmetil)oxi]-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida



Una suspensión de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-

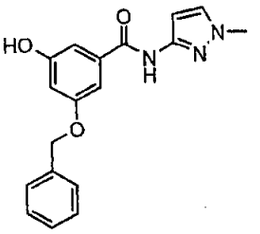
[(fenilmetil)oxi]benzamida (450 mg, 1.39 mmol), (3*R*)-tetrahidrofuran-3-il 4-metilbencenosulfonato (507 mg, 2.09 mmol) y carbonato de potasio (481 mg, 3.48 mmol) en acetonitrilo (5 mL) se agitó en un microondas Smith Creator a 160°C durante 3 horas. El disolvente se retiró *in vacuo* y se agregó acetato de etilo. Los orgánicos se lavaron con agua (40 mL), salmuera (40 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir una espuma amarilla, la cual se cromatografió en sílice, eluyendo con una gradiente de 0-100% acetato de etilo en iso-hexano, para producir el compuesto del título como una espuma blanca (452 mg).
^{1}H NMR δ ($CDCl_3$): 2.09 - 2.14 (1H, m), 2.14 - 2.24 (1H, m), 3.68 (3H, s), 3.86 - 3.91 (1H, m), 3.94 - 3.98 (3H, m), 4.89 (1H, s), 5.03 (2H, s), 6.64 (1H, t), 6.85 (1H, s), 6.96 (1H, d), 7.07 (1H, t), 7.27 (1H, m), 7.33 - 7.41 (5H, m), 9.31 (1H, s); *m/z* 394 $(M+H)^+$.

(3*R*)-Tetrahidrofuran-3-il 4-metilbencenosulfonato



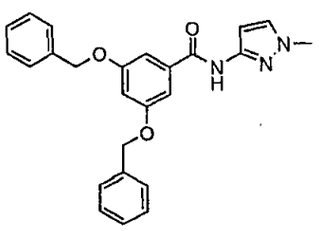
4-Tolueno sulfonil cloruro (1.65 g, 8.63 mmol) se agregó a una solución de *R*-3-hidroxitetrahidrofurano (0.8 g, 9.08 mmol) y piridina (0.88 mL, 10.9 mmol) en DCM (15 mL). La reacción se agitó a temperatura de la sala durante 72 horas. Se agregaron agua (10 mL) y 1M ácido clorhídrico (1 mL), y la mezcla se extrajo con DCM (15 mL). La capa orgánica se lavó con salmuera (20 mL), se secó ($MgSO_4$), se filtró y se redujo *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-50% acetato de etilo en isohexano, para producir el compuesto deseado (1.0 g). ^{1}H NMR δ ($CDCl_3$): 2.13 (m, 2H), 2.47 (s, 3H), 3.80-3.95 (m, 4H), 5.15 (m, 1H), 7.37 (d, 2H), 7.81 (d, 2H).

3-Hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi] benzamida



Una suspensión de *N*-(1-metil-1*H*-pirazol-3-il)-3,5-bis[(fenilmetil)oxi] benzamida (1.0 g, 2.42 mmol) se disolvió en etanol (12 mL) y se agregó formiato de amonio (229 mg, 3.63 mmol) en una porción. La reacción se cubrió con argón y se agregó 10% paladio sobre carbón activado (10 mg). Esta mezcla se calentó a 140°C durante 5 minutos en un microondas Smith Creator. El catalizador se extrajo completamente por filtración, y los volátiles se retiraron *in vacuo*, el residuo se cromatografió en sílice, eluyendo con una gradiente de 30-100% acetato de etilo en isohexano, para producir el compuesto del título como un sólido blanco (378 mg). ^{1}H NMR δ (d_6-DMSO): 3.78 (3H, s), 5.13 (2H, s), 6.55 - 6.57 (2H, m), 6.99 (1H, s), 7.17 (1H, s), 7.34 - 7.48 (5H, m), 7.60 (1H, d), 9.74 (1H, s), 10.70 (1H, s); *m/z* 324 $(M+H)^+$.

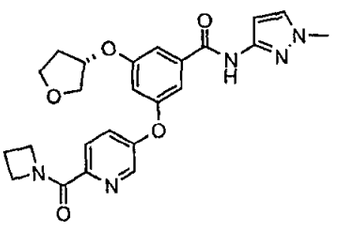
N-(1-Metil-1*H*-pirazol-3-il)-3,5-bis[(fenilmetil)oxi]benzamida



Cloruro de oxalilo (7.71 mL, 89.7 mmol) se agregó gota a gota a una suspensión de ácido 3,5-dibenciloxibenzoico (20.0 g, 59.8 mmol) en DCM (0.5 L) bajo argón. La reacción se agitó a temperatura de la sala durante 6 horas, tiempo luego del cual los volátiles se retiraron *in vacuo*. El residuo se tomó en DCM (300 mL), y se agregó gota a gota una solución de 1-metil-1*H*-pirazol-3-amina (5.81 g, 59.8 mmol) en DCM (50 mL). La solución resultante se agitó durante 16 horas a temperatura de la sala, tiempo luego del cual se había formado un precipitado. El sólido se aisló por filtración y se recristalizó de etanol para producir el compuesto del título como un

sólido blanco (14.8 g). ^{1}H NMR δ (d_6-DMSO): 3.84 (3H, s), 5.17 (4H, s), 6.59 (1H, d), 6.84 (1H, t), 7.33 - 7.46 (12H, m), 7.62 (1H, d), 10.83 (1H, s); *m/z* 414 $(M+H)^+$.

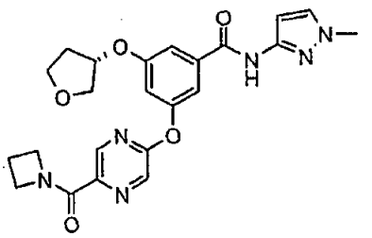
Ejemplo 26: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida



Una mezcla de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida (80 mg, 0.26 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (64 mg, 0.26 mmol), bromotris (trifenilfosfina)cobre(I) (49 mg, 0.05 mmol) y carbonato de cesio (257 mg, 0.78 mmol) en acetonitrilo (3 mL) se agitó en un microondas Smith Creator a 160°C durante 6 horas. El sólido se extrajo completamente por filtración y el disolvente se retiró *in vacuo*, y se agregó acetato de etilo (50 mL) al residuo. La fase orgánica se lavó con agua (20 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y el disolvente se retiró *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en DCM, para producir el compuesto del título como un sólido incoloro (58 mg). Este compuesto se cristalizó de acetato de etilo e isohexano empleando técnicas de difusión de vapor. ^{1}H NMR δ ($CDCl_3$): 2.11 - 2.17 (1H, m), 2.20 - 2.29 (1H, m), 2.32 - 2.39 (2H, m), 3.78 (3H, s), 3.88 - 3.93 (1H, m), 3.96 - 4.02 (3H, m), 4.25 (2H, t), 4.71 (2H, t), 4.97 (1H, t), 6.73 (1H, t), 6.79 (1H, s), 7.11 (1H, s), 7.22 (1H, s), 7.27 - 7.30 (1H, m), 7.36 - 7.39 (1H, m), 8.12 (1H, d), 8.32 (1H, d), 8.73 (1H, s); *m/z* 464 $(M+H)^+$.

La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describió anteriormente.

Ejemplo 27: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida

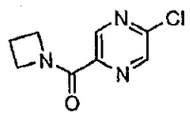


Una mezcla de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida (80 mg, 0.26 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (52 mg, 0.26 mmol) y carbonato de cesio (172 mg, 0.53 mmol) en acetonitrilo (3 mL) se agitó en un microondas Smith Creator a 160°C durante 1 hora. El disolvente se retiró *in vacuo* y se agregó acetato de etilo (50 mL) al residuo. La fase orgánica se lavó con agua (20 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice eluyendo con una gradiente de 0-10% metanol en DCM para producir el compuesto del título (36 mg, 31 %) como una espuma blanca. Este compuesto se cristalizó de acetato de etilo e isohexano empleando técnicas de difusión de vapor. ^{1}H NMR δ ($CDCl_3$): 2.12 - 2.19 (1H, m), 2.21 - 2.28 (1H, m), 2.34 - 2.42 (2H, m), 3.75 (3H, s), 3.88 - 3.93 (1H, m), 3.98 - 4.02 (3H, m), 4.23 (2H, t), 4.69 (2H, t), 4.95 - 4.97 (1H, m), 6.80 (1H, d), 6.87 (1H, t), 7.23 (1H, d), 7.27 - 7.30 (1H, m), 7.28 - 7.30 (1H, m), 8.34 (1H, d), 8.84 (1H, d), 8.98 (1H, s); *m/z* 465 $(M+H)^+$.

La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida se describió anteriormente.

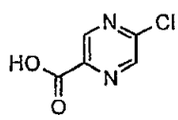
La preparación de 2-(azetidin-1-ilcarbonil)-5-cloropirazine se describe a continuación:

2-(Azetidin-1-ilcarbonil)-5-cloropirazina



Cloruro de oxalilo (1.55 mL, 17.48 mmol), seguido por DMF (2 gotas), se agregó a una mezcla de ácido 5-cloropirazin-2-carboxílico (2.31 g, 14.57 mmol) en DCM (40 mL). La reacción se agitó a temperatura de la sala durante 2 horas, tiempo luego del cual los volátiles se retiraron *in vacuo*. El residuo se tomó en DCM (40 mL) y azetidina (1.08 mL, 16.03 mmol), y se agregó trietilamina (4.46 mL, 32.06 mmol). La mezcla se agitó a temperatura de la sala durante 72 horas. Los volátiles se retiraron *in vacuo* y se agregó acetato de etilo (100 mL) al residuo. Los orgánicos se lavaron con agua (100 mL), ácido cítrico (50 mL), solución de bicarbonato de sodio saturado (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir un sólido amarillo. El residuo se cromatografió en sílice, eluyendo con una gradiente de 50 -100% acetato de etilo en isohexano, para producir el compuesto deseado como un sólido amarillo (2.38 g). ^{1}H NMR δ ($CDCl_3$): 2.35 - 2.42 (2H, m), 4.26 (2H, t), 4.67 (2H, t), 8.52 (1H, d), 9.09 (1H, d); *m/z* 198 $(M+H)^+$.

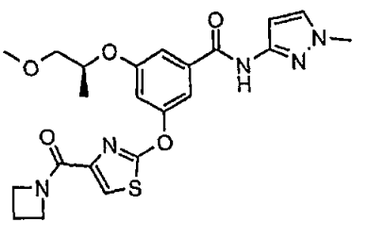
Ácido 5-cloropirazin-2-carboxílico



A una solución de metil-5-cloropirazin-2-carboxilato (120 mg, 0.70 mmol) en una mezcla de acetonitrilo (2 mL) y DMF (1 mL) se agregó cloruro de litio (295 mg, 6.95 mmol). La suspensión se calentó a 160°C durante 5 minutos en un microondas Smith Creator, tiempo luego del cual la reacción se diluyó con agua (10 mL). Se agregó una solución de bicarbonato de sodio saturado (20 mL) y la capa acuosa se extrajo dos veces con acetato de

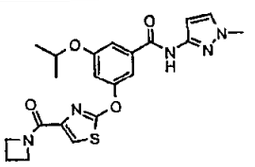
etilo (30 mL). Los orgánicos combinados se desecharon, y la capa acuosa se ajustó a pH 4 con 1N ácido clorhídrico. La fase acuosa se extrajo dos veces con acetato de etilo (20 mL), y los orgánicos combinados se lavaron con agua (2 x 20 mL), salmuera (10 mL) y se secaron ($MgSO_4$). Los volátiles se retiraron para producir el compuesto del título como un sólido incoloro (68 mg). ^{1}H. NMR δ ($CDCl_3$): 7.20 (1H, br s), 8.72 (1H, s), 9.21 - 9.21 (1H, m); *m/z* 157 $(M-H)^+$.

Ejemplo 28: 3-{[4-(Azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



Carbonato de cesio (488 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (153 mg, 0.5 mmol) y 4-(azetidin-1-ilcarbonil)-2-bromo-1,3-tiazol (206 mg, 0.75 mmol) en acetonitrilo (5 mL), y la mezcla agitada se calentó a 150°C en un aparato Biotage Initiator Microwave durante 8 horas. La mezcla se enfrió a temperatura y presión de la sala, se vertió en agua (75 mL) y se extrajo con acetato de etilo (3 x 25 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron a un residuo, el cual se cromatografió en sílice, eluyendo con acetato de etilo, para producir el material deseado (95 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.2 (m, 2H), 3.3 (s, 3H), 3.4-3.55 (m, 2H), 3.7 (s, 3H), 4.1 (t, 2H), 4.4 (t, 2H), 4.5 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.25 (s, 1H), 7.3 (s, 2H), 7.35 (s, 1H), 7.65 (s, 1H) y 8.8 (s, 1H); *m/z* 472 $(M+H)^+$.

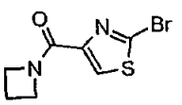
El siguiente compuesto se preparó en una forma análoga de 4-(azetidin-1-ilcarbonil)-2-bromo-1,3-tiazol y 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*- pirazol-3-il)benzamida

Ejemplo	Estructura	m/z	NMR
28a		442 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.2 (m, 2H), 3.7 (s, 3H), 4.1 (m, 2H), 4.4 (m, 2H), 4.5 (m, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.25 (d, 2H), 7.3 (s, 1H), 7.65 (s, 1H) y 9.0 (s, 1H).

La preparación de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol- 3-il)benzamida se describió anteriormente

La preparación de 4-(azetidin-1-ilcarbonil)-2-bromo-1,3-tiazol se describe a continuación:

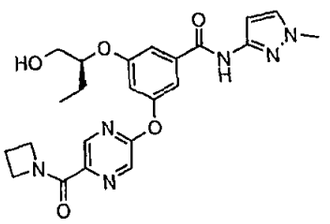
4-(Azetidin-1-ilcarbonil)-2-bromo-1,3-tiazol



A una solución de ácido 2-bromotiazol-5-carboxílico (752 mg, 3.62 mmol) en DCM (10 mL) se agregó lentamente cloruro de oxalilo (0.38 mL, 4.34 mmol) y luego DMF (1 gota). La mezcla se agitó durante 4 horas, luego de lo cual los orgánicos se retiraron *in vacuo*, y los residuos se destilaron bajo una temperatura fija con tolueno (10 mL). El material crudo se disolvió en DCM (10 mL) y lentamente se agregó a una suspensión agitada de clorhidrato de azetidina (404 mg, 4.34 mmol) y trietilamina (1.8 mL, 13 mmol) en DCM (25 mL). La mezcla se agitó a temperatura de la sala durante 2 horas antes de retirar los orgánicos *in vacuo*. El residuo se repartió en porciones entre acetato de etilo (50 mL) y agua (25 mL), la capa orgánica se lavó con salmuera (25 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 40% acetato de etilo en isohexano, para producir el compuesto deseado (500 mg). ^{1}H NMR

δ ($CDCl_3$): 2.3 (m, 2H), 4.15 (m, 2H), 4.6 (m, 2H) y 8.0 (s, 1H); *m/z* 249 $(M+H)^+$.

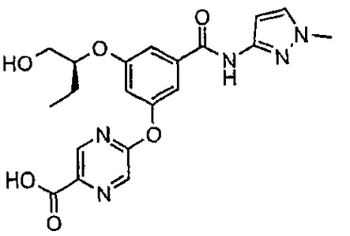
Ejemplo 29: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-1-(hidroximetil)propil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



Una solución de ácido 5-[(3-{[(1*S*)-1-(hidroximetil)propil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico (12 mg, 0.03 mmol), clorhidrato de azetidina (4 mg, 0.06 mmol), HATU (14 mg, 0.04 mmol) y DIPEA (0.02 mL, 0.11 mmol) en DMF (1 mL) se agitó a temperatura de la sala durante el fin de semana. Se agregó agua (15 mL) y la solución se extrajo con acetato de etilo (25 mL). La capa de acetato de etilo se lavó con salmuera (20 mL), se secó ($MgSO_4$), y se evaporó a un residuo, el cual se cromatografió mediante HPLC preparativa en fase reversa C18, eluyendo con 5-95% acetonitrilo (+0.2% TFA) en agua (+0.2% TFA), para proporcionar el producto requerido junto con un 15% de impureza co-eluyente (5 mg). ^{1}H NMR δ ($CDCl_3$): 0.92 (t, 3H), 0.97 (t, 0.45H), 1.69 (quintete, 2H), 1.76 (m, 0.3H), 2.34 (quintete, 2H), 3.76 (m, 2H), 3.86 (s, 3H), 4.23 (t, 2H), 4.49 (sextete, 1H), 4.66 (t, 2H), 4.77 (m, 0.15H), 6.93 (t, 1H), 6.99 (d, 1H), 7.34 (s, 1H), 7.46 (s, 1H), 7.50 (s, 1H), 8.29 (s, 1H), 8.78 (s, 1H), 10.68 (s, 1H), 10.78 (s, 0.15H); *m/z* 468 $(M+H)^+$ Los datos espectroscópicos son consistentes con 15% de la siguiente impureza 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(2*S*)-2-hidroxibutil] oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida.

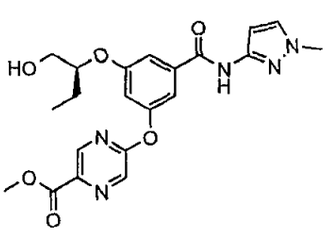
La preparación de ácido 5-[(3-{[(1*S*)-1-(hidroximetil)propil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico se describe a continuación:

Ácido 5-[(3-{[(1*S*)-1-(hidroximetil)propil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico



Monohidrato de hidróxido de litio (6 mg, 0.14 mmol) en agua (1 mL) se agregó a una solución de metil 5-[(3-{[(1*S*)-1-(hidroximetil)propil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato (25 mg, 0.06 mmol) en THF (1 mL). La mezcla se dejó agitando a temperatura de la sala durante 16 horas. El THF se retiró *in vacuo* y la solución resultante se repartió en porciones entre agua (10 mL) y acetato de etilo (25 mL), la capa de acetato de etilo se lavó con salmuera (10 mL) y se secó ($MgSO_4$). La capa acuosa se ajustó entonces a pH 7 mediante la adición de 1M ácido clorhídrico y se extrajo con acetato de etilo (25 mL). La capa de acetato de etilo se lavó con salmuera (10 mL) y se secó ($MgSO_4$). Los extractos de acetato de etilo se combinaron y se evaporaron para proporcionar el producto requerido (12 mg). *m/z* 428.44 $(M+H)^+$.

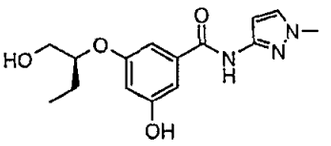
Metil 5-[(3-{[(1*S*)-1-(hidroximetil)propil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato



Metil 5-cloropirazin-2-carboxilato (104 mg, 0.60 mmol) y carbonato de cesio (467 mg, 1.43 mmol) se agregaron a una solución de 3-hidroxi-5-{[(1*S*)-1-(hidroximetil)propil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (175 mg, 0.570 mmol) en acetonitrilo (5 mL) y la mezcla se calentó en un reactor microondas a 160°C durante 330 minutos. El acetonitrilo se retiró *in*

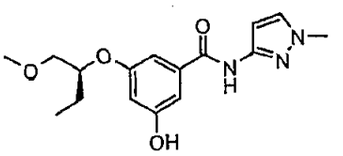
vacuo y el residuo se disolvió en acetato de etilo (25 mL), se lavó con agua (20 mL), salmuera (20 mL), se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió mediante HPLC preparativa en fase reversa C18, eluyendo con 5-95% acetonitrilo (+0.2% TFA) en agua (+0.2% TFA), para proporcionar el producto requerido (41 mg). ^{1}H NMR δ ($CDCl_3$): 0.97 (t, 3H), 1.78 (quintete, 2H), 3.82 (s, 3H), 3.91 (s, 3H), 4.52 (m, 3H), 4.66 (quintete, 1H), 6.59 (t, 1H), 6.89 (d, 1H), 7.05 (t, 1H), 7.15 (t, 1H), 8.19 (d, 1H), 8.79 (d, 1H), 9.86 (s, 1H); *m/z* 442 $(M+H)^+$.

3-Hidroxi-5-{[(1*S*)-1-(hidroximetil)propil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



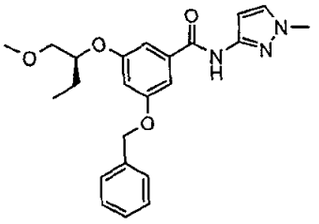
A una solución de 3-hidroxi-5-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (500 mg, 1.6 mmol) en acetonitrilo (25 mL) se agregó yodotrimetilsilano (1.11 mL, 7.8 mmol), y la mezcla resultante se agitó durante 16 horas. Se agregó solución de bicarbonato de sodio saturado (10 mL), la solución se agitó durante 10 minutos, (5 mL) se agregó tiosulfato de sodio acuoso saturado, luego el acetonitrilo se retiró *in vacuo*. La capa acuosa residual se extrajo con acetato de etilo (3 x 40 mL) y las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se evaporaron y se purificaron mediante cromatografía en columna, eluyendo con 85% acetato de etilo en isohexano, para producir el compuesto del título como una espuma incolora (405 mg). ^{1}H NMR δ (d_6-DMSO): 0.95 (t, 3H), 1.5-1.8 (m, 2H), 3.5 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 4.8 (t, 1H), 6.45 (s, 1H), 6.55 (s, 1H), 6.9 (s, 1H), 7.05 (s, 1H), 7.55 (s, 1H), 9.6 (s, 1H); *m/z* 306 $(M+H)^+$.

3-Hidroxi-5-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



A una solución de 3-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (4.6 g, 11 mmol) en 1:1 THF metanol (100 mL) se agregó 10% p/p paladio sobre carbón (450 mg) y la mezcla resultante se agitó bajo una atmósfera de hidrógeno durante 6 horas. La atmósfera se reemplazó con argón, y la mezcla se filtró y se evaporó para producir el compuesto del título como un sólido blanco (3.6 g). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 6.65 (s, 1H), 6.8 (s, 1H), 7.0 (m, 2H), 7.2 (m, 1H), 7.3 (s, 1H), 8.7 (s, 1H); *m/z* 320 $(M+H)^+$.

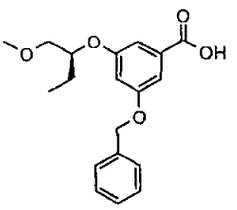
3-({(1*S*)-1-r(Metiloxi)metil]propil}oxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida



A una solución de ácido 3-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-5-[(fenilmetil)oxi]benzoico (4.75 g, 14.4 mmol) y 3-amino-1-metil-1*H*-pirazol (2.04 g, 21 mmol) en DMF (25 mL) se agregó HATU (8.53 g, 22.4 mmol), luego DIPEA (7.0 mL, 40 mmol), y la mezcla resultante se agitó durante 16 horas. La mezcla se repartió en porciones entre acetato de etilo (100 mL) y agua (30 mL). La capa orgánica se separó, se lavó con 1N ácido cítrico (30 mL), agua (30 mL), bicarbonato de sodio saturado (30 mL), agua (30 mL) y salmuera (30 mL), luego se secó ($MgSO_4$) y se evaporó. El residuo se purificó por cromatografía en columna, eluyendo con 50% acetato de etilo en isohexano, para producir el compuesto del título como un aceite incoloro (4.57 g). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 3.8 (s, 3H), 4.3 (m, 1H), 5.05 (s, 2H), 6.75 (s, 1H),

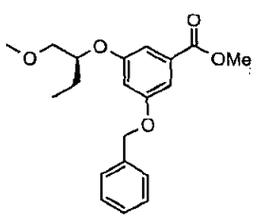
6.8 (s, 1H), 7.05 (d, 2H), 7.25 (s, 1H), 7.4 (m, 5H), 8.45 (s, 1H); *m/z* 410 $(M+H)^+$.

Ácido 3-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-5-[(fenilmetil)oxi]benzoico



A una solución de metil 3-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-5-[(fenilmetil)oxi]benzoato (6.85 g, 20 mmol) en 3:1 THF:metanol (100 mL) se agregó 1N solución de hidróxido de litio en agua (40 mL, 40 mmol), luego se agregaron 100 mL más de agua en porciones a intervalos, mientras la mezcla resultante se agitó durante 2 horas. Los disolventes orgánicos se retiraron por evaporación, y la solución turbia se filtró. El pH del filtrado se ajustó a 3 con la adición de 2 M ácido clorhídrico. Éste se extrajo con acetato de etilo (3 x 70 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$) y se evaporaron para producir el compuesto del título como un aceite incoloro, el cual se solidificó (6.36 g,). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.4 (s, 3H), 3.55 (m, 2H), 4.3 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.3-7.5 (m, 7H); *m/z* 329 $(M-H)^-$.

Metil 3-({(1*S*)-1-[(metiloxi)metil]propil}oxi)-5-[(fenilmetil)oxi] benzoato

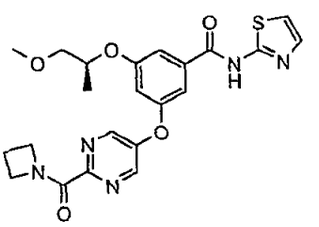


Una solución agitada de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (7.5 g, 29 mmol), ((*R*)-1-metoxi-butan-2-ol (3.76 g, 36.25 mmol) y trifenilfosfina (9.5 g, 36.25 mmol) en THF seco (75 mL) se enfrió en un baño helado, y se agregó gota a gota durante 30 minutos una solución de 40% DEAD en tolueno (15.8 mL, 36.25 mmol). La mezcla de reacción se dejó calentar lentamente a 10°C y se agitó durante 16 horas. El THF se evaporó y el

residuo se disolvió en 30% acetato de etilo en isohexano y se enfrió en hielo. El precipitado resultante se retiró por filtración y se lavó con 10% acetato de etilo en isohexano. El filtrado se evaporó y se purificó mediante cromatografía en columna, eluyendo con 10% acetato de etilo en isohexano, para producir el compuesto del título como un aceite incoloro (6.85 g). ^{1}H NMR δ ($CDCl_3$): 0.95 (t, 3H), 1.7 (m, 2H), 3.35 (s, 3H), 3.55 (m, 2H), 3.9 (s, 3H), 4.3 (m, 1H), 5.05 (s, 2H), 6.8 (s, 1H), 7.25 (m, 2H), 7.4 (m, 5H); *m/z* 345 $(M+H)^+$.

La preparación de (*R*)-1-metoxi-butan-2-ol se describió en la literatura [Coke, J. L.; Shue, R. S., *J. Org. Chem.* **38**, (1973), 2210-2211].
La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente.

Ejemplo 30: 3-{[2-(Azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-1,3-tiazol-2-ilbenzamida



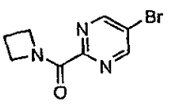
Una mezcla de 3-hidroxi-5-{[(1S)-2-metoxi-(1-metiletil)oxi}-*N*-1,3-tiazol-2-ilbenzamida (130 mg, 0.42 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopirimidina (113 mg, 0.46 mmol), carbonato de cesio (412 mg, 1.26 mmol) y bromotris(trifenilfosfina)cobre(I) (118 mg, 0.13 mmol) en DMA (5 mL) se agitó en un reactor microondas a 160°C durante 4 horas. Acetato de etilo (50 mL) se agregó al residuo y los orgánicos se lavaron con agua (20 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir un aceite marrón. El residuo se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en acetato de etilo, para producir el compuesto deseado (67 mg). ^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.38 (quintete, 2H), 3.40 (s, 3H), 3.49 - 3.61 (m,

2H), 4.29 (t, 2H), 4.59 - 4.67 (m, 3H), 6.92 (t, 1H), 6.98 (d, 1H), 7.23 (d, 1H), 7.44 (t, 1H), 7.49 (t, 1H), 8.54 (s, 2H), 11.96 (s, 1H); *m/z* 470 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-1,3-tiazol-2-ilbenzamida se describió anteriormente.

La preparación de 2-(azetidin-1-ilcarbonil)-5-bromopirimidina se describe a continuación:

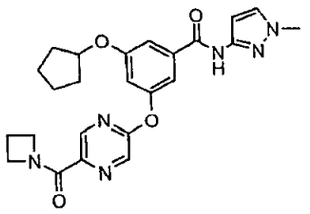
2-(Azetidin-1-ilcarbonil)-5-bromopirimidina



Cloruro de oxalilo (1.50 mL, 16.79 mmol), seguido por DMF (2 gotas), se agregó a una mezcla de ácido 5-bromopirimidin-2-carboxílico (2.86 g, 14.0 mmol) en DCM (40 mL). La reacción se agitó a temperatura de la sala durante 2 horas, los volátiles se retiraron *in vacuo*, y el residuo se disolvió en DCM (40 mL). Se agregaron clorhidrato de azetidina (1.44 g, 15.39 mmol), seguido por trietilamina (4.29 mL, 30.78 mmol), y la mezcla se agitó a temperatura de la sala durante 72 horas. La mezcla se concentró *in vacuo* y se agregó acetato de etilo (100 mL) al residuo. Los orgánicos se lavaron con agua (100 mL), ácido cítrico (50 mL), solución de bicarbonato de sodio saturado (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y el disolvente se retiró *in vacuo* para producir un sólido amarillo. El sólido se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado como un sólido amarillo (0.86 g).

La preparación de ácido 5-bromopirimidin-2-carboxílico se describe en la literatura (Solicitud Internacional de Patente WO 2005/028452).

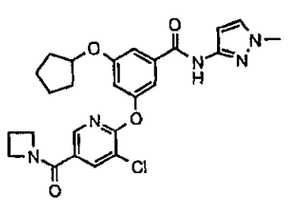
Ejemplo 31: 3{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-(ciclopentiloxi)-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



3-(Ciclopentiloxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (200 mg, 0.67 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (159 mg, 0.80 mmol) y carbonato de potasio (184 mg, 1.33 mmol) se disolvieron / suspendieron en acetonitrilo (3.5 mL). La mezcla de reacción se calentó durante 4 horas a 120°C en un reactor microondas. La mezcla se enfrió, se filtró y se concentró *in vacuo*. El producto crudo se cromatografió en sílice, eluyendo con 0-5% metanol en DCM, para proporcionar el producto requerido como una espuma blanca (282 mg).

^{1}H NMR δ (d_6-DMSO): 1.61 (m, 2H), 1.74 (m, 4H), 1.94 (m, 2H), 2.30 (m, 2H), 3.78 (s, 3H), 4.10 (t, 2H), 4.57 (t, 2H), 4.94 (m, 1H), 6.57 (d, 1H), 7.01 (t, 1H), 7.42 (m, 1H), 7.47 (m, 1H), 7.60 (d, 1H), 8.55 (d, 1H), 8.68 (d, 1H), 10.80 (s, 1H). *m/z* 463 $(M+H)^+$.

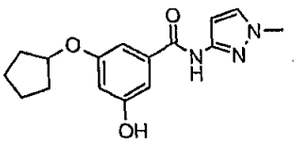
El siguiente compuesto se elaboró en una forma análoga de 3-(ciclopentiloxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina.

Ejemplo	Estructura	m/z	NMR
31a		496 $(M+H)^+$	δ: 1.69 (m, 2H), 1.82 (m, 4H), 2.03 (m, 2H), 2.34 (m, 2H), 3.99 (s, 3H), 4.14 (t, 2H), 4.45 (t, 2H), 5.03 (m, 1H), 6.65 (d, 1H), 7.06 (t, 1H), 7.47 (t, 1H), 7.54 (t, 1H), 7.68 (d, 1H), 8.30 (d, 1H), 8.42 (d, 1H), 10.87 (s, 1H).

Las preparaciones de 2-(azetidin-1-ilcarbonil)-5-cloropirazina y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describieron anteriormente.

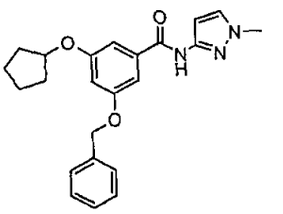
La preparación de 3-(ciclopentiloxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describe a continuación:

3-(Ciclopentiloxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



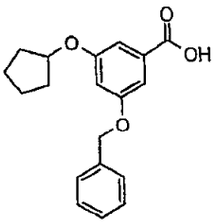
3-(Ciclopentiloxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi] benzamida (1.87g, 4.78 mmol) se disolvió en etanol (40 mL) y catalizador 10% paladio en carbón vegetal (102 mg) se agregó bajo argón. La reacción se agitó bajo una atmósfera de hidrógeno durante 86 horas, luego se filtró a través de Celite® y se concentró *in vacuo* a un sólido marrón claro (1.3Ig). ^{1}H NMR δ (d_6-DMSO): 1.54 (m, 2H), 1.76 (m, 4H), 1.96 (m, 2H), 2.75 (s, 1H), 3.83 (s, 3H), 4.91 (m, 1H), 6.49 (m, 1H), 6.61 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 7.65 (s, 1H), 9.73 (br s, 1H); *m/z* 302 $(M+H)^+$.

3-(Ciclopentiloxi)-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi] benzamida



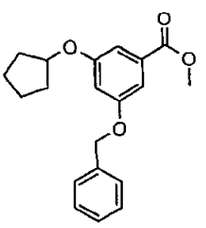
Ácido 3-(ciclopentiloxi)-5-[(fenilmetil)oxi]benzoico (3.14g, 10.0 mmol), 1-metil-1*H*-pirazol-3-amina (1.95g, 20 mmol) y HATU (4.95g, 13 mmol) se disolvieron en DMF (12.5 mL), luego se agregó DIPEA (3.49 mL, 20 mmol). La mezcla resultante se agitó a temperatura de la sala durante 20 horas. La mezcla se extinguió con agua (150 mL) y se extrajo con acetato de etilo (2 x 75 mL), se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para dejar un aceite amarillo. El residuo se cromatografió en sílice, eluyendo con 0-30% acetato de etilo en isohexano, para producir el producto deseado como una goma clara (1.87g). ^{1}H NMR δ ($CDCl_3$): 1.59 (m, 4H), 1.83 (m, 4H), 3.79 (s, 3H), 4.76 (m, 1H), 5.08 (s, 2H), 6.66 (t, 1H), 6.82 (m, 1H), 7.01 (m, 1H), 7.08 (m, 1H), 7.26 (m, 1H), 7.33 (m, 1H), 7.35-7.45 (m, 4H), 8.67 (s, 1H); *m/z* 392 $(M+H)^+$.

Ácido 3-(ciclopentiloxi)-5-[(fenilmetil)oxi]benzoico



Metil 3-(ciclopentiloxi)-5-[(fenilmetil)oxi]benzoato (9.25g, 28.34 mmol) se disolvió en THF (120 mL), y se agregó una solución de monohidrato de hidróxido de litio (3.49 g, 85.0 mmol) en agua (60 mL). La solución bi-fásica se agitó a temperatura de la sala durante 16 horas (LCMS indicó que el 80% de la reacción se había completado), se agregó metanol (15 mL) y la mezcla se agitó durante 4 horas más. El THF se retiró *in vacuo*, luego se agregó agua (40 mL) y se ajustó el pH a 7 con ácido clorhídrico. Se recolectó el sólido y se lavó concienzudamente con agua fría (8.85 g). ^{1}H NMR δ (d_6-DMSO): 1.64 (m, 2H), 1.76 (m, 4H), 1.96 (m, 2H), 4.89 (m, 1H), 5.19 (s, 2H), 6.80 (s, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.34-7.53 (m, 5H); *m/z* 311 $(M+H)^+$.

Metil 3-(ciclopentiloxi)-5-[(fenilmetil)oxi]benzoato

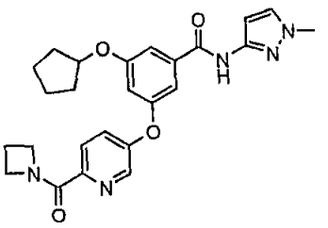


Metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (10 g, 38.7 mmol), 1-ciclopentanol (6.135 mL, 58.07 mmol) y trifenilfosfina (15.24g, 58.07 mmol) se agitaron bajo argón en THF (166 mL) y se enfriaron en un baño helado a 5°C. Se agregó DEAD (25.3 mL, 58.1 mmol) gota a gota a la mezcla, manteniendo la temperatura interna en el rango 5 - 10°C. Se continuó la agitación durante 16 horas. La mezcla se concentró *in vacuo*, se re-disolvió en acetato de etilo (60 mL) e isohexano (60 mL), el precipitado resultante se retiró, y la solución se concentró *in vacuo* para producir un aceite amarillo. El residuo se cromatografió en sílice, eluyendo con 0-30%

acetato de etilo en isohexano, para producir un aceite incoloro, el cual se recristalizó a un sólido blanco bajo vacío.
^{1}H NMR δ ($CDCl_3$): 1.62 (m, 2H), 1.71-1.98 (m, 6H), 3.90 (s, 3H), 4.76 (m, 1H), 5.08 (s, 2H), 6.69 (m, 1H), 7.16 (m, 1H), 7.23 (m, 1H), 7.29-7.44 (m, 5H); *m/z* 325 $(M+H)^+$.

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente.

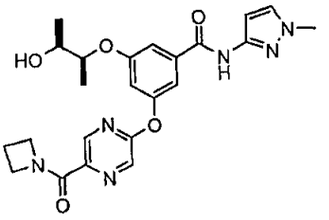
Ejemplo 32: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-(ciclopentiloxi)-*N*-(1-metil-1*H*-pirazol-3-il)benzamida



3-(Ciclopentiloxi)-5-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (200 mg, 0.67 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (193 mg, 0.80 mmol), bromotris(trifenilfosfina)cobre (186 mg, 0.2 mmol) y carbonato de cesio (230 mg, 0.70 mmol) se disolvieron / se suspendieron en DMA (3.5 mL). La mezcla de reacción se calentó durante 40 minutos a 200°C en un reactor microondas, luego se dejó enfriar, se filtró y se redujo *in vacuo*. El producto crudo se purificó por cromatografía en sílice, eluyendo con 0-100% acetato de etilo en isohexano, para producir el compuesto deseado como una espuma ligeramente amarilla (176 mg). ^{1}H NMR δ (d_6-DMSO): 1.61 (m, 2H), 1.73 (m, 4H), 1.94 (m, 2H), 2.28 (m, 2H), 3.78 (s, 3H), 4.08 (t, 2H), 4.59 (t, 2H), 4.95 (m, 1H), 6.56 (d, 1H), 6.88 (t, 1H), 7.28 (m, 1H), 7.43 (t, 1H), 7.56 (m, 1H), 7.59 (d, 1H), 7.99 (d, 1H), 8.41 (m, 1H), 10.85 (s, 1H); *m/z* 462 $(M+H)^+$.

Ejemplo 33 : 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida y

3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1:1)

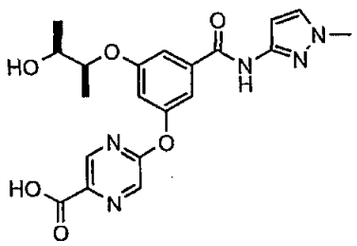


DIPEA (0.26 mL, 1.5 mmol) se agregó a una mezcla de ácido 5-[(3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino] carbonil} fenil)oxi]pirazin-2-carboxílico y ácido 5-[(3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino] carbonil}fenil)oxi]pirazin-2-carboxílico (1:1) (0.16 g, 0.37 mmol), clorhidrato de azetidina (71 mg, 0.75 mmol) y HATU (299 mg, 0.79 mmol) en DMF (5 mL) y se agitó a temperatura de la sala durante 72 horas. Acetato de etilo (40 mL) se agregó y la mezcla se lavó con agua (2 x 30 mL), salmuera (30 mL), se secó ($MgSO_4$), se filtró y se redujo *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-100% acetato de etilo en isohexano para producir la mezcla de diasteroisómeros del título como un aceite incoloro. La mezcla se separó mediante HPLC preparatoria quiral en una columna Chiralpak IA (250 mm x 20 mm) EGO 14, eluyendo con 30% etanol en *terc*-butilmetil éter. El primer diastereómero eluido, **Ejemplo 33a**, se aisló como una espuma blanca (18 mg). ^{1}H NMR δ ($CDCl_3$): 1.19 (d, 3H), 1.23 (d, 3H), 2.26 - 2.34 (m, 3H), 3.74 (s, 3H), 3.77 - 3.85 (m, 1H), 4.13 - 4.23 (m, 3H), 4.63 (t, 2H), 6.72 (d, 1H), 6.86 (t, 1H), 7.16 - 7.22 (m, 2H), 7.27 - 7.30 (m, 1H), 8.27 (d, 1H), 8.31 (s, 1H), 8.79 (d, 1H); *m/z* 467 $(M+H)^+$.

El segundo diastereómero eluido, **Ejemplo 33b**, se aisló como una espuma blanca (19 mg). ^{1}H NMR δ ($CDCl_3$): 1.19 (d, 3H), 1.22 (d, 3H), 2.27 - 2.36 (m, 3H), 3.73 (s, 3H), 3.76 - 3.84 (m, 1H), 4.13 - 4.22 (m, 3H), 4.62 (t, 2H), 6.72 (d, 1H), 6.86 (t, 1H), 7.17 - 7.19 (m, 1H), 7.21 (d, 1H), 7.28 (t, 1H), 8.26 (d, 1H), 8.40 (s, 1H), 8.79 (d, 1H); *m/z* 461 $(M+H)^+$.

La preparación de una mezcla de ácido 5-[(3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil) oxi]pirazin-2-carboxílico y ácido 5-[(3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil} fenil)oxi]pirazin-2-carboxílico (1:1) se describe a continuación:

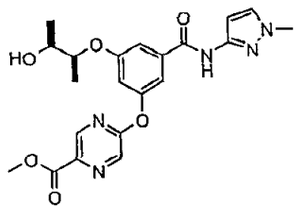
Ácido 5-[(3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico y ácido 5-[(3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxílico (1:1)



Monohidrato de hidróxido de litio (38 mg, 0.88 mmol) en agua (3 mL) se agregó a metil 5-[(3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)ammo]carbonil}fenil)oxi]pirazin-2-carboxilato y metil 5-[(3-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato (1:1) (0.26 g, 0.59 mmol) en THF (6 mL), y la mezcla se agitó a temperatura de la sala durante 72 horas. El THF se retiró *in vacuo*, y el residuo acuoso se ajustó a pH3 con ácido cítrico, luego se extrajo en acetato de etilo, se lavó con agua (30 mL), salmuera (30 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir el compuesto deseado como un sólido blanco (0.16 g). ^{1}H NMR δ (d_6-DMSO): 1.16 (d, 3H), 1.26 (d, 3H), 3.84 (s, 3H), 4.20 (m, 1H), 4.49 (m, 1H), 4.89 (d, 1H), 6.64 (d, 1H), 7.13 (t, 1H), 7.49 (s, 1H), 7.59 (s, 1H), 7.67 (d, 1H), 8.72 (d, 1H), 8.85 (d, 1H), 10.93 (s, 1H), 13.53 (s, 1H); *m/z* 426 $(M-H)^-$.

Metil 5-[(3-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato y

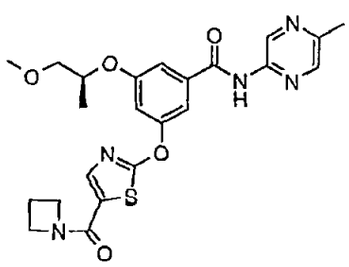
Metil 5-[(3-{[(1*S*,2*S*)-hidroxi-1-metilpropil]oxi}-5-{[(1-metil-1*H*-pirazol-3-il)amino]carbonil}fenil)oxi]pirazin-2-carboxilato (1:1)



Una mezcla de 3-hidroxi-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (1:1) (230 mg, 0.75 mmol), metil 5-cloropirazin-2-carboxilato (195 mg, 1.13 mmol) y carbonato de potasio (208 mg, 1.51 mmol) en acetonitrilo (5 mL) se agitó en un reactor microondas a 130°C durante 3 horas. El disolvente se retiró *in vacuo* y se agregó agua. La mezcla se acidificó, se extrajo en acetato de etilo, y los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo* para producir una espuma amarilla (265 mg), la cual se empleó en el siguiente paso sin purificación posterior. ^{1}H NMR δ ($CDCl_3$): 1.29 (m, 6H), 1.99 (s, 1H), 3.80 (s, 3H), 3.90 (quintete, 1H), 4.05 (s, 3H), 4.25 (quintete, 1H), 6.82 (d, 1H), 6.95 (t, 1H), 7.30 (m, 2H), 7.39 (s, 1H), 8.55 (s, 1H), 8.55 (s, 1H), 8.86 (s, 1H); *m/z* 442 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*R*,2*R*)-2-hidroxi-1-metilpropil] oxi}-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y 3-hidroxi-5-{[(1*S*,2*S*)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1*H*-pirazol-3-il)benzamida (1:1) se describió anteriormente.

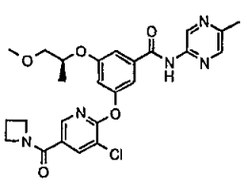
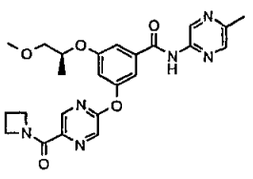
Ejemplo 34: 3-{[5-(Azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il) benzamida

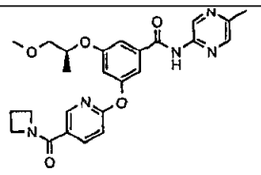
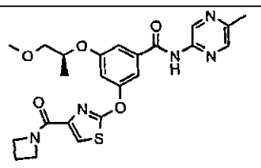
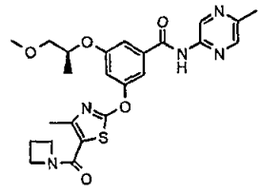
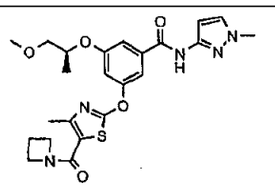


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Carbonato de cesio (489 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida (159 mg, 0.5 mmol) y 5-(azetidin-1-ilcarbonil)-2-cloro-1,3-tiazol (152 mg, 0.75 mmol) en acetonitrilo (5 mL), y la mezcla agitada se calentó a 120°C en un reactor microondas durante 1 hora. La mezcla se enfrió a temperatura de la sala y a presión ambiente, el acetonitrilo se evaporó *in vacuo*, el residuo se repartió en porciones entre agua (25 mL) y acetato de etilo (50 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con acetato de etilo, para producir el producto deseado (181 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.35 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.1 - 4.4 (m, 4H), 4.55 (m, 1H), 7.0 (d, 1H),7.35 (d, 1H), 7.45 (s, 1H), 7.45 (s, 1H), 8.05 (s, 1H), 8.4 (s, 1H) y 9.45 (s, 1H). *m/z* 484 $(M+H)^+$.

Los siguientes compuestos se sintetizaron en una forma análoga de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida o 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida y el heterociclo halogenado apropiado:

Ejemplo	Estructura	m/z	NMR
34a		512 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.1 - 4.35 (m, 4H), 4.55 (m, 1H), 6.9 (d, 1H), 7.2 (d, 1H), 7.35 (s, 1H), 8.05 (s, 1H), 8.1 (s, 1H), 8.2 (d, 1H), 8.3 (s, 1H) y 9.45 (s, 1H).
34b* **		479 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.2 (t, 2H), 4.55 (m, 1H), 4.65 (t, 2H), 6.9 (d, 1H), 7.25 (d, 1H), 7.35 (d, 1H), 8.05 (s, 1H), 8.3 (s, 1H), 8.45 (s, 1H) 8.8 (s, 1H) y 9.45 (s, 1H).

34c		478 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.15-4.35 (m, 4H), 4.55 (m, 1H), 6.8 (d, 1H), 6.95 (d, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 8.0 (dd, 1H), 8.05 (s, 1H), 8.35 (d, 1H), 8.5 (s, 1H) y 9.5 (s, 1H).
34d		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.2 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.15 (t, 2H), 4.4 (t, 2H), 4.55 (m, 1H), 7.0 (d, 1H), 7.3 (d, 1H), 7.45 (s, 1H), 7.65 (s, 1H), 8.05 (s, 1H), 8.4 (s, 1H) y 9.45 (s, 1H).
34e		498 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.25 (m, 2H), 2.45 (s, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45-3.55 (m, 2H), 4.1 - 4.2 (t, 4H), 4.55 (m, 1H), 7.0 (d, 1H), 7.35 (d, 2H), 8.05 (s, 1H), 8.4 (s, 1H) y 9.45 (s, 1H).
34f**		486 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.25 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4-3.55 (m, 2H), 3.7 (s, 3H), 4.1 -4.2 (t, 4H), 4.5 (m, 1H), 6.7 (s, 1H), 6.95 (s, 1H), 7.2 (d, 1H), 7.3 (d, 2H) y 8.6 (s, 1H).

** el compuesto se cristalizó parcialmente de éter dietílico; punto de fusión (mpt): iniciación de la fusión 80.7°C

*** **Ejemplo 34b**, 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il) benzamida, se preparó también de la siguiente manera.

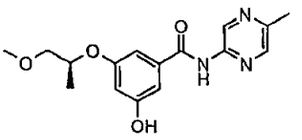
Una mezcla de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida (25.4 g, 80.0 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (17.4 g, 88.0 mmol) y carbonato de potasio (33.1 g, 240 mmol) en acetonitrilo (254 mL) se calentó a 60°C durante 24 horas. El disolvente se retiró por evaporación y el residuo se repartió en porciones

entre acetato de etilo (15 volúmenes) y agua (10 vol). Las capas se separaron, la capa acuosa se extrajo posteriormente en acetato de etilo (2 x 10 volúmenes) y los orgánicos combinados se lavaron con agua (2 x 5 volúmenes), salmuera (5 vol), se secaron ($MgSO_4$), se filtraron, se concentraron *in vacuo*. El residuo se cromatografió en sílice, eluyendo con acetato de etilo, para producir el compuesto deseado como una espuma (33.7 g). El material puro se disolvió en *terc*-butilmetil éter caliente (30 volúmenes), se ensemilló con una muestra cristalina genuina (las semillas se aislaron de una cristalización a pequeña escala, donde el material se disolvió en una cantidad mínima de *terc*-butilmetil éter caliente, luego se agregó isohexano y el matraz se rayó para promover la cristalización) y se agitó de un día para otro. La mezcla se enfrió y el material cristalino (iniciación de la fusión 110.3°C) se recolectó por filtración (29.1 g).

^{1}H NMR δ (d_6-DMSO): 1.27 (d, 3H), 2.30 (quintete, 2H), 2.49 (s, 3H), 3.31 (s, 3H), 3.47 - 3.56 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.79 (td, 1H), 7.13 (t, 1H), 7.48 (td, 1H), 7.57 (td, 1H), 8.36 (d, 1H), 8.56 (d, 1H), 8.69 (d, 1H), 9.26 (d, 1H), 11.00 (s, 1H); *m/z* 479 $(M+H)^+$. Esta forma cristalina pudo convertirse en una forma cristalina diferente poniendo aproximadamente 30mg de material en un frasquito con un agitador magnético (***"a magnetic flea"***), y agregando aproximadamente 1 mL de agua. Se agregaron a esto unas cuantas gotas (3) de metanol, y el frasquito se selló con una tapa. La suspensión (***"slurry"***) se dejó entonces agitando sobre una placa magnética a temperatura de la sala (25°C). Después de 3 días, la muestra se retiró de la placa, se quitó la tapa y se dejó secar la suspensión bajo condiciones ambiente. La nueva forma cristalina (iniciación de la fusión 110.2°C) se mostró diferente mediante análisis XRPD.

El compuesto del título puede cristalizarse también agitando una suspensión del compuesto en agua. La preparación de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida se describe a continuación:

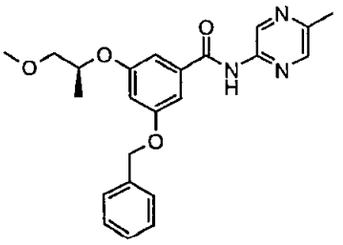
3-Hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida



10% Paladio en carbón vegetal (700 mg) se agregó a una solución de 3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)-5-[(fenilmetil) oxi]benzamida (7.0 g, 17.2 mmol) en etanol (125 mL), y la mezcla se agitó a temperatura de la sala bajo una atmósfera de hidrógeno durante 4 horas. El catalizador se retiró por filtración y el etanol se evaporó *in vacuo*. El residuo se cristalizó de acetato de etilo para producir el compuesto deseado (4.22 g). ^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 - 3.5 (m, 2H), 4.5 (m, 1H), 6.3 (br, 1H), 6.55 (s, 1H), 6.9 (s, 1H), 6.95 (s, 1H), 8.05 (s, 1H), 8.45 (s, 1H) y 9.5 (s, 1H). *m*/z 318 $(M+H)^+$.

Esta reacción se llevó igualmente a cabo empleando metanol como disolvente y utilizando una presión de hidrógeno de 5 bares.

3-{[(1*S*)-1-Metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)-5-[(fenilmetil)oxi]benzamida



Cloruro de oxalilo (2.1 mL, 24.0 mmol) se agregó a una solución de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico (6.32 g, 20.0 mmol) en DCM (100 mL), y la mezcla se agitó a temperatura de la sala durante 4 horas. La mezcla se evaporó *in vacuo* a un residuo, el cual se tomó en DCM (25 mL) y se agregó a una mezcla agitada de 2-amino-5-metilpirazina (2.29 g, 21.0 mmol) y piridina (1.94 mL, 24.0 mmol) en DCM (100 mL) a 5°C - 10°C. La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo*. El residuo se repartió en porciones

entre agua (50 mL) y acetato de etilo (150 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el compuesto deseado (7.0 g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 - 3.5 (m, 2H), 4.5 (m, 1H), 5.0 (s, 2H), 6.7 (s, 1H), 7.0 (s, 1H), 7.05 (s, 1H), 7.35 (m, 5H), 8.05 (s, 1H), 8.3 (s, 1H) y 9.5 (s, 1H). *m/z* 408 $(M+H)^+$.

La preparación de 2-amino-5 metilpirazina se describe en la literatura [*Tetrahedron Lett.* **2002**, 9287].

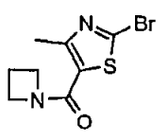
La preparación de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil]oxi}benzoico se describió anteriormente.

La preparación de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describió anteriormente.

Las preparaciones de los heterociclos halogenados 5-(azetidin-1-ilcarbonil)-2-cloro-1,3-tiazol, 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina, 2-(azetidin-1-ilcarbonil)-5-cloropirazina, 5-(azetidin-1-ilcarbonil)-2-cloropiridina y 4-(azetidin-1-ilcarbonil)-2-bromo-1,3-tiazol se describieron anteriormente.

La preparación de 5-(azetidin-1-ilcarbonil)-2-bromo-4-metil-1,3-tiazol, empleado en **Ejemplos 34e-f**, se describe a continuación:

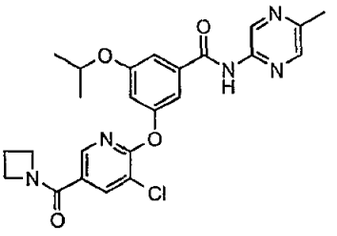
5-(Azetidin-1-ilcarbonil)-2-bromo-4-metil-1,3-tiazol



Cloruro de oxalilo (0.47 mL; 5.41 mmol) se agregó a una solución de ácido 2-bromo-4-metil-1,3-tiazol-5-carboxílico (1.0 g; 4.5 mmol) en DCM (25 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo*, el residuo se destiló bajo una temperatura fija con tolueno (2 x 5 mL) y se agregó a una solución de clorhidrato de azetidina (503 mg; 5.41 mmol) y trietilamina (2.3 mL; 16.2 mmol) en DCM (50 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se

evaporó *in vacuo*, y el residuo se repartió en porciones entre agua (75 mL) y acetato de etilo (150 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 40% acetato de etilo en isohexano, para producir un sólido, el cual se cristalizó de acetato de etilo / isohexano para producir el compuesto deseado (490 mg). ^{1}H NMR δ ($CDCl_3$): 2.35 (m, 2H), 2.55 (s, 3H) y 4.1 (t, 4H).

Ejemplo 35: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida

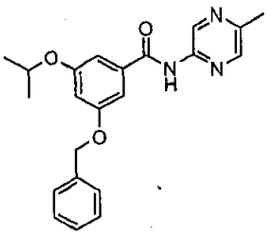


Carbonato de cesio (489 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida (144 mg, 0.5 mmol) y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (173 mg, 0.75 mmol) en acetonitrilo (5 mL) y la mezcla agitada se calentó a 120°C en un reactor microondas durante 1 hora. La mezcla se enfrió a temperatura de la sala y a presión ambiente, el acetonitrilo se evaporó *in vacuo*, el residuo se repartió en porciones entre agua (25 mL) y acetato de etilo (50 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 75% acetato de etilo en isohexano, para producir el compuesto deseado (167 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.3 (m, 2H), 2.5 (s, 3H), 4.1 - 4.3 (m, 4H), 4.55 (m, 1H), 6.85 (d, 1H), 7.2 (d, 1H), 7.3 (s, 1H), 8.05 (s, 1H), 8.1 (s, 1H), 8.2 (s, 1H) 8.3 (s, 1H) y 9.45 (s, 1H). *m/z* 482 $(M+H)^+$.

Los siguientes compuestos se prepararon en forma análoga de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida y el heterociclo halogenado apropiado:

compuesto deseado (3.42g). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.5 (s, 3H), 4.5 (m, 1H), 5.8 (br, 1H), 6.5 (d, 1H), 6.9 (d, 1H), 6.95 (d, 1H), 8.05 (s, 1H), 8.4 (s, 1H) y 9.5 (s, 1H). *m/z* 288 $(M+H)^+$.

3-[(1-Metiletil)oxi]-*N*-(5-metilpirazin-2-il)-5-[(fenilmetil)oxi]benzamida



Cloruro de oxalilo (2.1 mL, 24.0 mmol) se agregó a una solución de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico (5.72 g, 20.0 mmol) en DCM (100 mL) y la mezcla se agitó temperatura de la sala durante 4 horas. La mezcla se evaporó *in vacuo* a un residuo, el cual se tomó en DCM (25 mL) y se agregó a una mezcla agitada de 2-amino-5-metilpirazina (2.29 g, 21.0 mmol) y piridina (1.94 mL, 24.0 mmol) en DCM (100 mL) a 5°C - 10°C. La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo* a un residuo, el cual se repartió en porciones entre agua (50 mL) y acetato de etilo (150 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 30% acetato de etilo en isohexano, y se cristalizó de acetato de etilo / isohexano para producir el compuesto deseado (5.52 g).

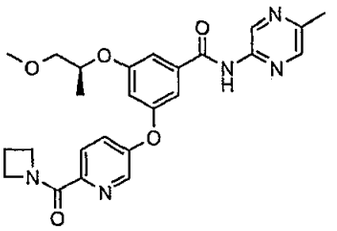
^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.5 (s, 3H), 4.5 (m, 1H), 5.0 (s, 2H), 6.6 (s, 1H), 6.95 (s, 1H), 7.0 (s, 1H), 7.35 (m, 5H), 8.05 (s, 1H), 8.3 (s, 1H) y 9.5 (s, 1H). *m/z* 378 $(M+H)^+$.

Las preparaciones de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico y 2-amino-5-metilpirazina se describieron anteriormente.

Las preparaciones de los heterociclos halogenados 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina, 2-(azetidin-1-ilcarbonil)-5-cloropirazina, 5-(azetidin-1-

ilcarbonil)-2-cloropiridina y 5-(azetidin-1-ilcarbonil)-2-bromo-4-metil-1,3-tiazol se describieron anteriormente.

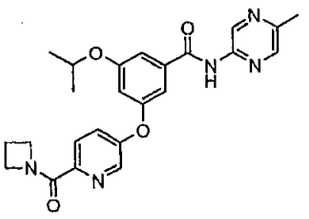
Ejemplo 36: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida



Carbonato de cesio (489 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida (159 mg, 0.5 mmol) y 2-(azetidin-1-ilcarbonil)-5-bromopiridina (181 mg, 0.75 mmol) y bromotris(trifenilfosfina)cobre (93 mg, 0.1 mmol) en DMA (5 mL), y la mezcla agitada se calentó a 160°C en un reactor microondas durante 4 horas. La mezcla se enfrió a temperatura de la sala y a presión ambiente, se repartió en porciones entre agua (75 mL) y acetato de etilo (50 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con acetato de etilo, para producir el compuesto deseado, que se cristalizó de éter (45 mg, iniciación de la fusión 113.8°C). El compuesto puede cristalizarse asimismo de acetato de etilo, dando lugar a una forma cristalina alternativa (iniciación de la fusión 132.7°C). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.3 (m, 2H), 2.5 (s, 3H), 3.3 (s, 3H), 3.45 - 3.55 (m, 2H), 4.2 (t, 2H), 4.55 (m, 1H), 4.65 (t, 2H), 6.75 (d, 1H), 7.05 (d, 1H), 7.25 (s, 1H), 7.3 (d, 1H), 8.0 (s, 1H), 8.05 (d, 1H), 8.25 (d, 1H), 8.3 (s, 1H) y 9.45 (s, 1H). *m/z* 478 $(M+H)^+$.

Las preparaciones de 2-(azetidin-1-ilcarbonil)-5-bromopiridina y 3-hidroxi-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida se describieron anteriormente.

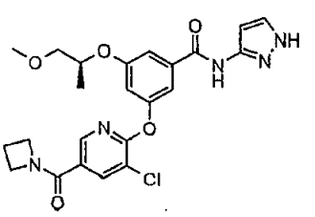
Ejemplo 37: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida



Carbonato de cesio (489 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida (144 mg, 0.5 mmol) y 2-(azetidin-1-ilcarbonil)-5-bromopiridina (181 mg, 0.75 mmol) y bromotris(trifenilfosfina)cobre (93 mg, 0.1 mmol) en DMA (5 mL), y la mezcla agitada se calentó a 160°C en un reactor microondas durante 4 horas. La mezcla se enfrió a temperatura de la sala y a presión ambiente, se repartió en porciones entre agua (75 mL) y acetato de etilo (50 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con 75% acetato de etilo en isohexano, para producir el compuesto deseado (cristalizado de éter) (72 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 2.3 (m, 2H), 2.5 (s, 3H), 4.2 (t, 2H), 4.5 (m, 1H), 4.65 (t, 2H), 6.7 (s, 1H), 7.05 (s, 1H), 7.2 (s, 1H), 7.3 (d, 1H), 8.0 (br, 2H), 8.3 (br, 2H) y 9.45 (s, 1H). *m/z* 448 $(M+H)^+$. Mpt (iniciación de la fusión) 125.7°C.

Las preparaciones de 2-(azetidin-1-ilcarbonil)-5-bromopiridina y 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida se describieron anteriormente.

Ejemplo 38: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-1*H*-pirazol-3-ilbenzamida

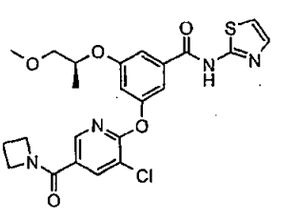


Una mezcla de 1,1-dimetiletil 3-{[(3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)carbonil]amino}-1*H*-pirazol-1-carboxilato (196 mg, 0.5 mmol), 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (128 mg, 0.55 mmol) y carbonato de potasio (138 mg, 1.0 mmol) en acetonitrilo (5 mL) se agitó en un reactor microondas a 120°C durante 4 horas. El disolvente se retiró *in vacuo* y el residuo se repartió en porciones entre acetato de etilo y agua. La capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado como una espuma blanca (142 mg).

^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.31 (quintete, 2H), 3.33 (s, 3H), 3.43 - 3.53 (m, 2H), 4.11 - 4.33 (m, 4H), 4.54 (q, 1H), 6.78 (s, 1H), 6.86 (s, 1H), 7.24 (s, 1H), 7.33 (s, 1H), 7.42 (s, 1H), 8.06 (d, 1H), 8.12 (s, 1H), 9.98 (s, 1H); *m/z* 486 $(M+H)^+$.

Las preparaciones de 1,1-dimetiletil 3-{[(3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}fenil)carbonil]amino}-1*H*-pirazol-1-carboxilato y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describieron anteriormente.

Ejemplo 39: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-1,3-tiazol-2-ilbenzamida

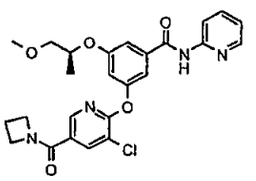
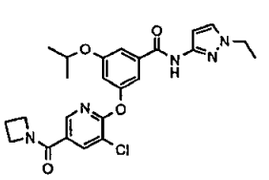


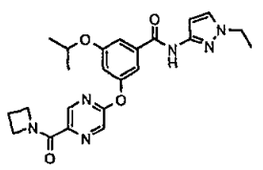
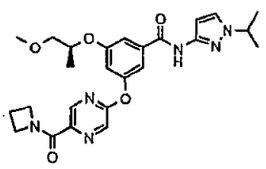
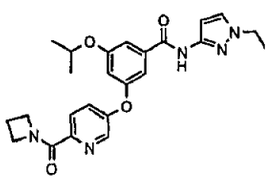
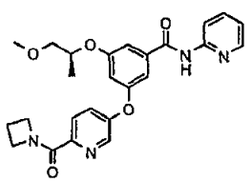
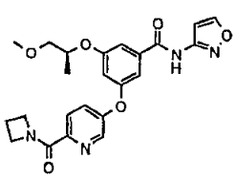
DIPEA (0.129 mL) se agregó a una suspensión de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi) etil]oxi}benzoico (168 mg), HATU (190 mg) y 2-aminotiazol (40 mg) en DMF (2 mL), y la mezcla se agitó a temperatura de la sala durante 16 horas. Se agregó agua (30 mL), y la mezcla se extrajo con acetato de etilo (3 x 20 mL). Los extractos orgánicos combinados se lavaron con salmuera. se

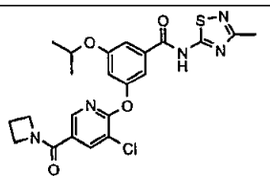
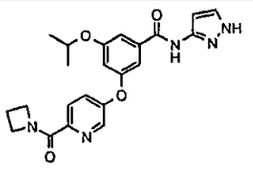
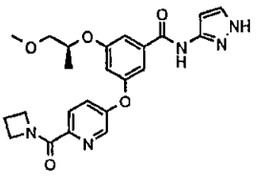
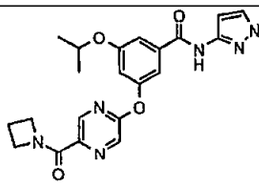
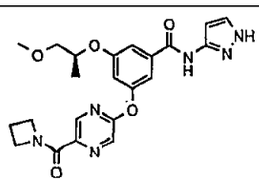
secaron ($MgSO_4$), y se evaporaron a un residuo, el cual se cromatografió en sílice, eluyendo con 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (75 mg).

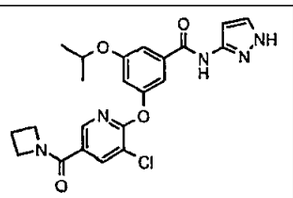
^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.31 (quintete, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 4.12 - 4.33 (m, 4H), 4.55 (q, 1H), 6.91 (d, 1H), 6.95 (s, 1H), 7.30 (s, 1H), 7.31 (d, 1H), 7.40 (s, 1H), 8.08 (s, 1H), 8.16 (s, 1H); *m/z* 503 $(M+H)^+$

Los siguientes compuestos se elaboraron en una forma análoga de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzoico, ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico o ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi] benzoico y el aminoheterociclo apropiado.

Ejemplo	Estructura	m/z	NMR
39a		497 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.32 (quintete, 2H), 3.34 (s, 3H), 3.41-3.56 (m, 2H), 4.11 -4.34 (m, 4H), 4.55 (q, 1H), 6.90 (s, 1H), 7.00 (t, 1H), 7.22 (s, 1H), 7.34 (s, 1H), 7.68 (t, 1H), 8.08 (s, 1H), 8.19 (s, 1H), 8.23 (s, 1H), 8.27 (d, 1H), 8.37 - 8.56 (m, 1H)
39b		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 6H), 1.39 (t, 3H), 2.31 (quintete, 2H), 4.00 (q, 2H), 4.11 - 4.34 (m, 4H), 4.54 (quintete, 1H), 6.73 (s, 1H), 6.81 (s, 1H), 7.14 (s, 1H), 7.24 (s, 2H), 8.09 (s, 1H), 8.18 (s, 1H), 8.39

			(s, 1H)
39c		451 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 6H), 1.39 (t, 3H), 2.31 (quintete, 2H), 3.99 (q,-2H), 4.19 (t, 2H), 4.53 (quintete, 1H), 4.61 (t, 2H), 6.72 (s, 1H), 6.80 (s, 1H), 7.14 (s, 1H), 7.25 (s, 2H), 8.25 (s, 1H), 8.36 (s, 1H), 8.79 (s, 1H)
39d		495 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 1.41 (d, 6H), 2.31 (quintete, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 4.19 (t, 2H), 4.30 (quintete, 1H), 4.54 (q, 1H), 4.62 (t, 2H), 6.71 (s, 1H), 6.86 (s, 1H), 7.18 (s, 1H), 7.28 (s, 1H), 7.30 (s, 1H), 8.25 (s, 1H), 8.33 (s, 1H), 8.79 (s, 1H)
39e		450 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 1.39 (t, 3H), 2.28 (quintete, 2H), 4.00 (q, 2H), 4.18 (t, 2H), 4.52 (quintete, 1H), 4.64 (t, 2H), 6.65 (s, 1H), 6.71 (s, 1H), 7.00 (s, 1H), 7.16 (s, 1H), 7.25 (s, 1H), 7.30 (d, 1H), 8.04 (d, 1H), 8.25 (s, 1H), 8.32 (s, 1H)
39f		463 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.28 (quintete, 2H), 3.34 (s, 3H), 3.43 - 3.54 (m, 2H), 4.18 (t, 2H), 4.56 (q, 1H), 4.64 (t, 2H), 6.76 (s, 1H), 7.03 (q, 1H), 7.10 (s, 1H), 7.27 (s, 1H), 7.31 (d, 1H), 7.71 (t, 1H), 8.05 (d, 1H), 8.23 (s, 1H), 8.26 (s, 1H), 8.29 (d, 1H), 8.59 (s, 1H)
39g		453 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.27 (quintete, 2H), 3.32 (s, 3H), 3.41 - 3.53 (m, 2H), 4.17 (t, 2H), 4.54 (q, 1H), 4.63 (t, 2H), 6.78 (s,

			1H), 7.11 (s, 1H), 7.15 (s, 1H), 7.27 (s, 1H), 7.29 (d, 1H), 8.03 (d, 1H), 8.18 (s, 1H), 8.25 (s, 1H), 9.43 (s, 1H)
39h		488 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.22 (d, 6H), 2.16 (quintete, 2H), 2.41 (s, 3H), 3.95 (t, 2H), 4.26 (t, 2H), 4.67 (quintete, 1H), 7.05 (s, 1H), 7.43 (s, 1H), 7.52 (s, 1H), 8.15 (s, 1H), 8.25 (s, 1H), 13.32 (s, 1H)
39i*		422 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.27 (quintete, 2H), 4.16 (t, 2H), 4.51 (quintete, 1H), 4.62 (t, 2H), 6.68 (s, 1H), 6.72 (s, 1H), 7.08 (s, 1H), 7.23 (s, 1H), 7.28 (d, 1H), 7.46 (s, 1H), 7.99 (d, 1H), 8.24 (s, 1H), 9.25 (s, 1H)
39j*+		452 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.28 (quintete, 2H), 3.33 (s, 3H), 3.42 - 3.55 (m, 2H), 4.16 (t, 2H), 4.54 (q, 1H), 4.62 (t, 2H), 6.73 (s, 1H), 6.75 (s, 1H), 7.12 (s, 1H), 7.28 (d, 1H), 7.32 (s, 1H), 7.43 (s, 1H), 8.00 (d, 1H), 8.24 (s, 1H), 9.78 (s, 1H)
39k*++		423 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.31 (quintete, 2H), 4.19 (t, 2H), 4.52 (quintete, 1H), 4.61 (t, 2H), 6.76 - 6.78 (m, 2H), 7.19 (s, 1H), 7.27 (s, 1H), 7.37 (s, 1H), 8.29 (s, 1H), 8.74 (s, 1H), 10.03 (s, 1H)
39l*		453 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.31 (quintete, 2H), 3.33 (s, 3H), 3.42 - 3.54 (m, 2H), 4.18 (t, 2H), 4.53 (q, 1H), 4.61 (t, 2H), 6.78 (s,

			1H), 6.83 (s, 1H), 7.22 (s, 1H), 7.35 (s, 2H), 8.31 (s, 1H), 8.73 (s, 1H), 10.38 (s, 1H)
39m*		456 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.28 (d, 6H), 2.31 (quintete, 2H), 4.15 (t, 2H), 4.25 (t, 2H), 4.53 (quintete, 1H), 6.79 (s, 2H), 7.20 (s, 1H), 7.26 (s, 1H), 7.33 (s, 1H), 8.08 (s, 1H), 8.10 (s, 1H), 10.44 (s, 1H)

* Las reacciones se llevaron a cabo empleando 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato como el aminoheterociclo, los productos resultantes se disolvieron en acetonitrilo (4 mL) y etanol (0.5 mL) y se calentaron en un reactor microondas a 150°C durante 12 minutos.

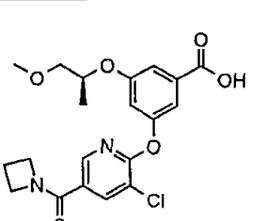
Las mezclas se dejaron enfriar, luego se concentraron *in vacuo* para producir los productos deseados.

+ Este compuesto se cristalizó de acetato de etilo e isohexano empleando técnicas de difusión de vapor.

++ Este compuesto se cristalizó de acetonitrilo, punto de fusión (iniciación de la fusión) 108.5 °C.

La preparación de 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se describió anteriormente. La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi} benzoico se da a continuación:

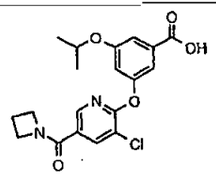
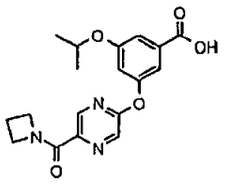
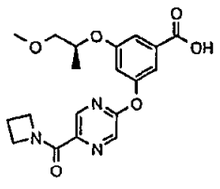
Ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico



Una mezcla de metil 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]benzoato (240 mg, 0.1 mmol), 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (278 mg,

1.2 mmol) y carbonato de potasio (276 mg, 2.0 mmol) en DMA (5 mL) se agitó a 120°C durante 16 horas. La solución se vertió en agua (30 mL) y se acidificó con 1N ácido clorhídrico antes de extraerse con acetato de etilo (3 x 20 mL). Los orgánicos combinados se lavaron con salmuera (20 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoato (como se evidenció por los datos LCMS únicamente *m/z* 435 $(M+H)^+$) como un aceite parduzco (550 mg). El metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoato crudo (434 mg, 1 mmol) se disolvió en THF (15 mL) y metanol (5 mL), luego se agregó 1N solución de hidróxido de litio acuoso (2 mL), seguido por la adición gota a gota de agua hasta que se obtuvo una solución clara. La mezcla se agitó se agitó durante 4 horas a temperatura de la sala y los orgánicos se retiraron por evaporación. La solución acuosa se filtró, se extrajo con acetato de etilo (10 mL) y la capa acuosa se acidificó con 2N ácido clorhídrico. La capa acidificada se extrajo con acetato de etilo (3 x 30 mL) y los extractos orgánicos combinados se lavaron con agua (10 mL), salmuera (10 mL) y se concentraron *in vacuo* para producir el compuesto deseado como un aceite pálido (375 mg). ^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.32 (quintete, 2H), 3.34 (s, 3H), 3.42 - 3.55 (m, 2H), 4.13 - 4.34 (m, 4H), 4.54 (q, 1H), 6.93 (s, 1H), 7.40 (s, 1H), 7.48 (s, 1H), 8.08 (s, 1H), 8.19 (s, 1H), *m/z* 421 $(M+H)^+$.

Ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil) oxi]benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]benzoico y ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzoico se elaboraron en una forma análoga de metil 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]benzoato o metil 3-hidroxi-5-[(1-metiletil)oxi]benzoato y el heterociclo halogenado apropiado.

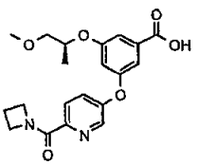
Estructura	m/z	NMR
	391 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 6H), 2.31 (quintete, 2H), 4.11 - 4.35 (m, 4H), 4.53 (quintete, 1H), 6.87 (s, 1H), 7.37 (s, 1H), 7.42 (s, 1H), 8.09 (s, 1H), 8.19 (s, 1H)
	358 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.28 (6H, d), 2.26 -2.34 (2H, quin), 4.10 (2H, t), 4.56 (2H, t), 4.65 - 4.71 (1H, quin), 7.11 (1H, t), 7.29 (1H, s), 7.33 (1H, s), 8.53 (1H, s), 8.66 (1H, s)
	388 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.31 (quintete, 2H), 3.33 (s, 3H), 3.41 - 3.55 (m, 2H), 4.20 (t, 2H), 4.50 - 4.57 (m, 1H), 4.62 (t, 2H), 6.92 (t, 1H), 7.39 (s, 1H), 7.49 (s, 1H), 8.25 (s, 1H), 8.78 (s, 1H)

La preparación de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]benzoico se describe a continuación:

Ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi] benzoico

Una mezcla de metil 3-hidroxi-5-[(1-metiletil)oxi]benzoato (0.84 g, 4 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (1.16 g, 4.8 mmol), carbonato de cesio (3.92 g, 1.2 mmol) y bromotris(trifenilfosfina) cobre(I) (744 mg, 0.8 mmol) en DMA (20 mL) se agitó en un reactor microondas a 160°C durante 6 horas. La mezcla se diluyó con agua (100 mL), se lavó con acetato de etilo (2 x 20 mL), y la capa acuosa se filtró, luego se acidificó con 2N ácido clorhídrico. La capa ácida se extrajo con acetato de etilo (3 x 50 mL), los orgánicos combinados se lavaron con agua (2 x 20 mL), salmuera (20 mL), se secaron ($MgSO_4$), y el disolvente se retiró *in vacuo*. El residuo se trituró con éter para producir el compuesto deseado como un sólido blanco (1.06 g). ^{1}H NMR δ (d_6-DMSO): 1.28 (d, 6H), 2.28 (quintete, 2H), 4.08 (t, 2H), 4.59 (t, 2H), 4.69 (quintete, 1H), 6.98 (t, 1H), 7.10 (s, 1H), 7.28 (s, 1H), 7.56 (d, 1H), 7.99 (d, 1H), 8.41 (s, 1H); *m/z* 357 $(M+H)^+$.

Ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico se preparó en una forma análoga de 2-(azetidin-1-ilcarbonil)-5-bromopiridina y metil 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]benzoato.

Estructura	m/z	NMR
	387 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.25 (d, 3H), 2.28 (quintete, 2H), 3.33 (s, 3H), 3.40 - 3.54 (m, 2H), 4.20 (t, 2H), 4.53 (quintete, 1H), 4.64 (t, 2H), 6.79 (t, 1H), 7.25 (s, 1H), 7.42 (s, 1H), 7.99 - 8.11 (m, 1H), 8.19-8.35 (m, 1H)

Las preparaciones de metil 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil) oxi]benzoato, metil 3-hidroxi-5-[(1-metiletil)oxi]benzoato y los heterociclos halogenados apropiados se describieron anteriormente.

3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-*N*-1*H*-pirazol-3-ilbenzamida, **Ejemplo 39k**, se preparó asimismo en la siguiente manera de 1,1-dimetiletil 3-[({3-hidroxi-5-[(1-metiletil) oxi]fenil}carbonil)amino]-1*H*-pirazol-1-carboxilato.

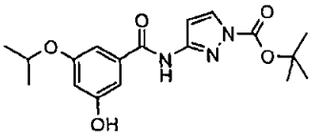
1,1-Dimetiletil 3-[({3-hidroxi-5-[(1-metiletil)oxi]fenil}carbonil)amino]-1*H*-pirazol-1-carboxilato (56.3 g, 0.16 mol) se disolvió en acetonitrilo (500 mL) y se cargó en un recipiente fijo de 3L. Se agregó carbonato de potasio – abertura de malla 325 - (64.5 g, 0.47 mol), seguido por 2-(azetidin-1-ilcarbonil)-5-cloropirazina (33.5 g, 0.17 mol) con un lavado de carga de 100 mL de acetonitrilo. La mezcla se agitó rápidamente y se calentó a 60°C bajo nitrógeno. Se agregó más acetonitrilo (250 mL), después de 1.5 horas, seguido por la adición de DMF (150 mL) para disolver el material sólido residual. La reacción se agitó de un día para otro, luego se dejó enfriar a temperatura de la sala y se filtró. El filtrado se concentró bajo vacío para retirar el acetonitrilo, y la solución residual se vertió en agua (1500 mL) agitando simultáneamente. El sólido precipitado se filtró, se disolvió en

DCM (560 mL), se lavó con 1:1 salmuera / solución acuosa saturada de bicarbonato de sodio (2 x 500 mL) y se secó ($MgSO_4$). La solución orgánica se filtró y se agregó TFA (50 mL). La solución se agitó a temperatura de la sala durante 3 horas. Se agregó más TFA (50 mL) y la mezcla se agitó a 30°C durante 3 horas más, luego a temperatura de la sala de un día para otro. El disolvente se retiró bajo vacío y el residuo se destiló bajo una temperatura fija con tolueno. El residuo aceitoso anaranjado se disolvió en acetato de etilo (500 mL) y se lavó con una solución saturada de bicarbonato de sodio (2 x 500 mL), salmuera (500 mL), se secó ($MgSO_4$) y se concentró para dejar un sólido ceroso amarillo pálido (64 g). El sólido se trituró con acetato de etilo (200 mL) a 45°C durante 2 horas, se filtró, se lavó con acetato de etilo y se secó en un horno de vacío a 40°C de un día para otro para dejar un sólido blanco (52 g). El sólido crudo se cromatografió en columna de sílice, eluyendo con una mezcla de una solución 7N de amoníaco en metanol en DCM (gradiente 0.5 - 6.5% metanol), para producir el material puro deseado [puro 1] (23.6 g, 99.1% puro por HPLC), y material menos puro se recuperó de fracciones mixtas y licores previos (34.5 g, 82.8% puro por HPLC). El material impuro se disolvió en DCM (50 mL), y se cristalizó un sólido blanco. El sólido se retiró mediante filtración y se lavó con DCM para producir el material deseado puro [puro 2] (6.5 g, 98.3% puro por HPLC). El filtrado se cromatografió en columna en sílice, eluyendo con una solución 7N de amoníaco en metanol en DCM (gradiente 0 - 5% metanol), para producir el material deseado [puro 3] (18.3 g, 98.7% puro por HPLC). Puros 1, 2 & 3 se combinaron (48.4 g) y cargaron en un recipiente fijo de 3L. Acetato de etilo (500 mL, 10 vol) se agregó y la mezcla se calentó a reflujo agitando simultáneamente, se agregó más acetato de etilo (400 mL, 8 volúmenes) y el material sólido restante se retiró mediante filtración en caliente. El filtrado se enfrió a 60°C y se agregó isohexano (250 mL) gota a gota. La suspensión se enfrió a 20°C durante aproximadamente 1 hora y luego se agitó a temperatura de la sala de un día para otro. La suspensión se filtró y el sólido se lavó con isohexano (2 x 200 mL), luego se secó en un horno de

vacío a 40°C para dejar un sólido blanco (34.5 g). Este sólido se secó posteriormente en un horno de vacío a 60°C de un día para otro para dejar el compuesto deseado como un polvo blanco (33.1 g). Ésta es una forma de cristal diferente de la descrita previamente, punto de fusión (iniciación de la fusión) 113.8°C.

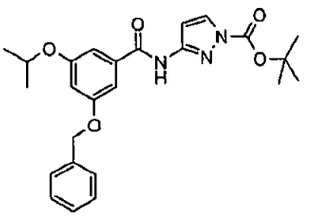
La preparación de 2-(azetidin-1-ilcarbonil)-5-cloropirazina se describió anteriormente. La preparación de 1,1-dimetiletil 3-[({3-hidroxi-5-[(1-metiletil)oxi]fenil}carbonil)amino]-1*H*-pirazol-1-carboxilato se describe a continuación.

1,1-Dimetiletil 3-[({3-hidroxi-5-[(1-metiletil)oxi]fenil}carbonil) amino]-1*H*-pirazol-1-carboxilato



1,1-Dimetiletil 3-[({3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi] fenil}carbonil)amino]-1*H*-pirazol-1-carboxilato (76.4 g, 0.17 mol) se disolvió en etanol (750 mL, 10 vol), y se agregó 10% paladio sobre carbón vegetal (humedecido con agua) (7.5 g). La mezcla se hidrogenó durante 18 horas a 25°C y a una presión de 5 bares. El catalizador se retiró por filtración a través de Celite®, y la torta se lavó con metanol (250 mL). El filtrado combinado se concentró bajo vacío para dejar un sólido espumoso color crema, el cual se cromatografió en sílice, eluyendo con 10-70% acetato de etilo en isohexano, para producir el material deseado como un sólido espumoso blanco (56.4 g). ^{1}H NMR δ ($CDCl_3$): 1.30 (d, 6H), 1.64 (s, 9H), 4.49 - 4.55 (m, 1H), 6.67 (t, 1H), 6.98 (d, 2H), 7.10 (d, 1H), 8.02 (d, 1H), 9.21 (s, 1H); *m/z* 360 $(M-H)^-$.

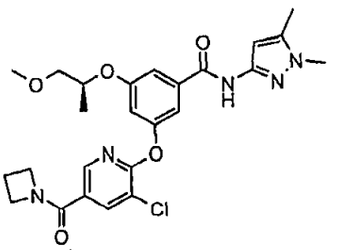
1,1-Dimetiletil 3-[({3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]fenil}carbonil) amino]-1*H*-pirazol-1-carboxilato



Una solución de cloruro de oxalilo (76 mL, 0.87 mol) en DCM (125 mL) se agregó gota a gota a una suspensión de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico (50 g, 0.17 mol) y DMF (1 mL) en DCM (300 mL). La reacción se agitó a temperatura de la sala durante 2 horas, luego el disolvente se retiró bajo vacío y el residuo se destiló bajo temperatura fija con tolueno (200 mL). El residuo aceitoso se disolvió en piridina seca (100 mL) y la mezcla se agregó, durante 5 minutos, a una solución de 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato (38.4 g, 0.21 mol) en piridina seca (325 mL) bajo nitrógeno. La reacción se agitó a temperatura de la sala durante 1 hora, el disolvente se retiró bajo vacío y el residuo se destiló bajo temperatura fija con tolueno. El residuo se repartió en porciones entre DCM (500 mL) y agua (500 mL), y la capa orgánica se lavó con una solución acuosa saturada de bicarbonato de sodio (500 mL), salmuera (500 mL) y se secó ($MgSO_4$). La solución orgánica se concentró bajo vacío, y el residuo se destiló dos veces bajo temperatura fija con tolueno para dejar una resina anaranjada (88.8 g). La resina se cromatografió en sílice, eluyendo con 25-50% acetato de etilo en isohexano, para producir el material deseado como una espuma amarillo pálido (76.4 g). ^{1}H NMR δ ($CDCl_3$): 1.33 (d, 6H), 1.56 (s, 9H), 4.49 - 4.55 (m, 1H), 5.04 (s, 2H), 6.69 (t, 1H), 7.00 (t, 1H), 7.06 - 7.07 (m, 1H), 7.17 (d, 1H), 7.32 - 7.45 (m, 5H), 8.04 (d, 1H), 9.48 (s, 1H); *m/z* 450 $(M-H)^-$.

Las preparaciones de ácido 3-[(1-metiletil)oxi]-5-[(fenilmetil)oxi]benzoico y 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se describieron anteriormente.

Ejemplo 40: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-*N*-(1,5-dimetil-1*H*-pirazol-3-il)-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi} benzamida

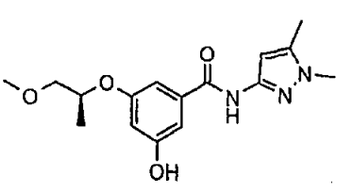


Una solución de *N*-(1,5-dimetil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida (0.62 mmol) en acetonitrilo (5 mL) se trató con carbonato de potasio (1.24 mmol) y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (0.68 mmol), antes de calentar a 120°C en un reactor microondas durante 4.5 horas. La mezcla se evaporó *in vacuo*, antes de repartirla en porciones entre DCM (20 mL) y agua (20 mL). Los orgánicos se evaporaron *in vacuo*, luego se cromatografiaron en sílice, eluyendo con 0-10% metanol en acetato de etilo, para producir el compuesto deseado como una espuma blanca (160 mg).

^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 2.24 (s, 3H), 2.26 (m, 2H), 3.30 (s, 3H), 3.50 (m, 2H), 3.66 (s, 3H), 4.05 (t, 2H), 4.37 (t, 2H), 4.78 (m, 1H), 6.42 (s, 1H), 7.03 (t, 1H), 7.38 (t, 1H), 7.51 (t, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 10.76 (s, 1H); *m/z* 514, 516 $(M+H)^+$.

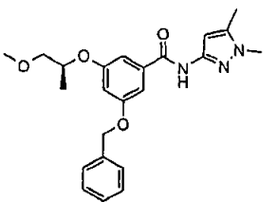
La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describió anteriormente. La preparación de *N*-(1,5-dimetil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzamida se describe a continuación:

N-(1,5-Dimetil-1*H*-pirazol-3-il)-3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi) etil]oxi}benzamida



Una solución de N-(1,5-dimetil-1*H*-pirazol-3-il)-3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil)oxi]benzamida (2.57 mmol) en etanol (40 mL), bajo argón, se trató con 10% paladio sobre carbón (100 mg, se humedeció con 0.1 mL de agua y 1 mL de etanol). El matraz se vació y se llenó con hidrógeno, este procedimiento se repitió 4 veces. La mezcla se dejó agitando a temperatura de la sala de un día para otro bajo una atmósfera de hidrógeno, luego la reacción se filtró a través de Celite® y la torta se lavó con etanol (50 mL) y acetato de etilo (50 mL). Las capas orgánicas combinadas se evaporaron *in vacuo* para producir el compuesto deseado como una espuma blanca (597 mg). ^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.25 (s, 3H), 3.31 (s, 3H), 3.47 (m, 2H), 3.66 (s, 3H), 4.66 (m, 1H), 6.40 (s, 1H), 6.46 (t, 1H), 6.95 (t, 1H), 7.06 (t, 1H), 9.60 (s, 1H), 10.49 (s, 1H); *m/z* 320 $(M+H)^+$.

<u>*N*-(1,5-Dimetil-1*H*-pirazol-3-il)-3-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil)oxi]benzamida</u>



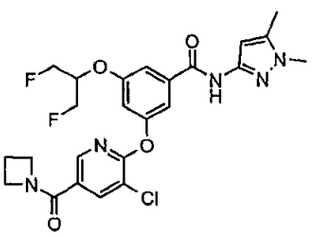
Una solución de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil] oxi}benzoico (4.11 mmol) en DMF (10 mL) se trató con la 1,5-dimetil-1*H*-pirazol-3-ilamina (4.52 mmol), DIPEA (5.93 mmol) y HATU (3.85 mmol) y se agitó a temperatura de la sala de un día para otro, bajo una atmósfera de argón. La mezcla se vertió en agua (100 mL) y se extrajo con acetato de etilo (3 x 100 mL). La capa orgánica se lavó con salmuera (20 mL) y se evaporó *in vacuo* antes de la cromatografía en sílice, eluyendo con 20-80% acetato de etilo en isohexano, para producir el compuesto deseado como un aceite amarillo (1.05 g).

^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.25 (s, 3H), 3.30 (s, 3H), 3.48 (m, 2H), 3.67 (s, 3H), 4.71 (m, 1H), 5.16 (s, 2H), 6.42 (s, 1H), 6.73 (t, 1H), 7.20

(t, 1H), 7.26 (t, 1H), 7.34 (m, 1H), 7.41 (m, 2H), 7.46 (m, 2H)$_3$ 10.62 (s, 1H); *m/z* 410 $(M+H)^+$

La preparación de ácido 3-[(1*S*)-2-metoxi-(1-metiletil)oxi]-5-{[fenilmetil] oxi}benzoico se describió anteriormente.
La 1,5-dimetil-1*H*-pirazol-3-ilamina se preparó de acuerdo con la ruta divulgada en la literatura [*J. Het. Chem.*, (1982), *19*, 1267].

Ejemplo 41: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-*N*-(1,5-dimetil-1*H*-pirazol-3-il)-5-{[2-fluoro-1-fluorometil)etil]oxi} benzamida

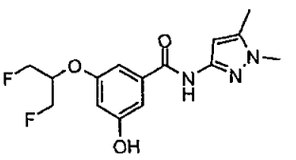


Una solución de *N*-(1,5-dimetil-1*H*-pirazol-3-il)-3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxibenzamida (0.61 mmol) en acetonitrilo (5 mL), se trató con el carbonato de potasio (1.23 mmol) y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (0.68 mmol), antes de calentar a 120°C en un reactor microondas durante 4 horas. La mezcla se filtró y se evaporó *in vacuo* antes de cromatografiarse en sílice, eluyendo con 0-5% metanol en acetato de etilo, para producir el compuesto deseado como una espuma blanca (175 mg).
^{1}H NMR δ (d_6-DMSO): 2.27 (m, 5H), 3.66 (s, 3H), 4.06 (t, 2H), 4.37 (t, 2H), 4.65 (m, 1H), 4.73 (m, 1H), 4.77 (m, 1H), 4.85 (m, 1H), 5.10 (m, 1H), 6.42 (s, 1H), 7.16 (t, 1H), 7.45 (t, 1H), 7.60 (t, 1H), 8.23 (d, 1H), 8.35 (d, 1H), 10.71 (s, 1H) *m/z* 520 $(M+H)^+$.

La preparación de 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describió anteriormente. La preparación de *N*-(1,5-dimetil-1*H*-pirazol-3-il)-3-{[2-

fluoro-1-(fluorometil)etil]oxi}-5-hidroxibenzamida se describe a continuación:

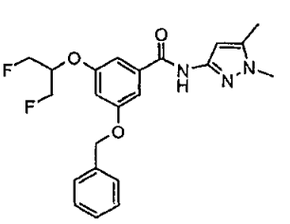
N-(1,5-Dimetil-1*H*-pirazol-3-il)-3-{[2-fluoro-1-(fluorometil)etil]oxi} -5-hidroxibenzamida



Una solución de *N*-(1,5-dimetil-1*H*-pirazol-3-il)-3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi]benzamida (1.89 mmol) en etanol (30 mL) se trató con 10% paladio sobre carbón (78 mg, humedecido con 1 mL etanol). El matraz se vació y se llenó con hidrógeno y este procedimiento se repitió 4 veces más. La mezcla se dejó agitando a temperatura de la sala de un día para otro bajo una atmósfera de hidrógeno, luego la mezcla se filtró a través de Celite® y la torta se lavó con etanol (50 mL) y acetato de etilo (50 mL). Los orgánicos combinados se evaporaron *in vacuo* para producir el compuesto deseado como una espuma blanca (613 mg).

^{1}H NMR δ (d_6-DMSO): 2.52 (s, 3H), 3.66 (s, 3H), 4.66 (m, 2H), 4.77 (m, 2H), 4.97 (m, 1H), 6.41 (s, 1H), 6.56 (t, 1H), 7.02 (m, 1H), 7.15 (t, 1H), 10.52 (s, 1H); *m/z* 326 $(M+H)^+$.

N-(1,5-Dimetil-1*H*-pirazol-3-il)-3-{[2-fluoro-1-(fluorometil)etil]oxi)-5-[(fenilmetil)oxi]benzamida

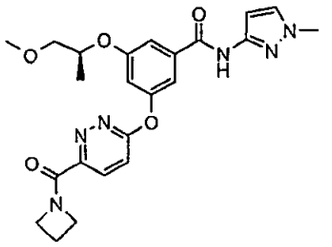


Una solución de ácido 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil) oxi]benzoico (2.96 mmol) en DMF (5 mL) se trató con 1,5-dimetil-1*H*-pirazol-3-ilamina (3.11 mmol), DIPEA (5.93 mmol) y HATU (3.85 mmol),

y se agitó a temperatura de la sala de un día para otro. La mezcla se vertió en agua (100 mL) y se extrajo con acetato de etilo (3 x 75 mL). Los orgánicos se lavaron con salmuera, se secaron ($MgSO_4$) y se evaporaron *in vacuo* antes de la cromatografía en sílice, eluyendo con 50-100% acetato de etilo en isohexano, para producir el compuesto deseado como un cristal incoloro (784 mg). ^{1}H NMR δ (d_6-DMSO): 2.81 (s, 3H), 3.67 (s, 3H), 4.66 (m, 2H), 4.78 (m, 2H), 5.04 (m, 1H), 5.69 (s, 2H), 6.43 (s, 1H), 6.85 (t, 1H), 7.28 (m, 1H), 7.32 (m, 1H), 7.35 (m, 1H), 7.41 (m, 2H), 7.47 (m, 2H), 10.64 (s, 1H); *m/z* 416 $(M+H)^+$.

Las preparaciones de ácido 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi]benzoico y 1,5-dimetil-1*H*-pirazol-3-ilamina se describieron anteriormente.

Ejemplo 42: 3-{[6-(Azetidin-1-ilcarbonil)piridazin-3-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(1-metil-1*H*-pirazol-3-il) benzamida



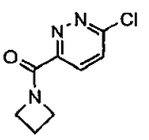
Una mezcla de 3-(azetidin-1-ilcarbonil)-6-cloropiridazina (45 mg, 0.23 mmol), 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida (70 mg, 0.23 mmol) y carbonato de potasio (63 mg, 0.46 mmol) en acetonitrilo (3 mL) se agitó en un microondas Smith Creator a 130°C durante 1 hora. El sólido se extrajo completamente por filtración y el disolvente se retiró *in vacuo*. El residuo se purificó mediante HPLC preparativa de fase reversa, eluyendo con 5 - 95% acetonitrilo en agua (+ 0.2% TFA), seguido por paso a través de un cartucho Silicycle Si-Carbonate, eluyendo con metanol, para producir el producto deseado como un sólido incoloro (97 mg). ^{1}H NMR δ ($CDCl_3$): 1.34 (3H, d), 1.66 (3H, s), 2.33 - 2.41 (2H, m), 3.40 (3H, s), 3.48 - 3.52 (1H, m), 3.56 - 3.60 (1H, m),

3.79 (3H, s), 4.27 (2H, d), 4.58 - 4.62 (1H, m), 4.76 (2H, t), 6.79 (1H, d), 6.97 (1H, t), 7.25 - 7.29 (3H, m), 7.35 - 7.36 (1H, m), 8.26 - 8.28 (1H, m), 8.49 (1H, s); *m/z* 467 $(M+H)^+$.

La preparación de 3-hidroxi-5-[(1*S*)-2-metoxi-(1-metiletil)oxi]-*N*-(1-metil-1*H*-pirazol-3-il)benzamida se describió anteriormente.

La preparación de 3-(azetidin-1-ilcarbonil)-6-cloropiridazina se describe a continuación:

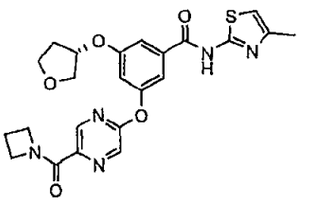
3-(Azetidin-1-ilcarbonil)-6-cloropiridazina



Oxicloruro de fósforo (50 mL) se agregó a ácido 6-hidroxipiridazin-3-carboxílico (9.82 g, 70.05 mmol) y la solución resultante se calentó a reflujo. Después de 45 minutos la solución se dejó enfriar, y el exceso de oxicloruro de fósforo se retiró bajo presión reducida. THF (50 mL) se agregó al residuo negro, y la solución resultante se enfrió a 0°C. Trietilamina (9.77 mL, 70.05 mmol) y azetidina (4.0 g, 70.05 mmol) se agregaron gota a gota. La mezcla resultante se dejó calentar a temperatura de la sala y se agitó de un día para otro. Los volátiles se retiraron bajo presión reducida y se agregó agua (50 mL), luego el residuo se ajustó a pH8 empleando solución de hidróxido de sodio. La capa acuosa se extrajo cinco veces con acetato de etilo, los orgánicos combinados se secaron ($MgSO_4$) y el disolvente se retiró para proporcionar el producto crudo como un aceite oscuro. Una muestra se purificó mediante HPLC preparativa, eluyendo con 5 - 95% acetoniltrilo en agua (+ 0.2% TFA), y se produjo el compuesto del título como un sólido incoloro (135 mg).

^{1}H NMR δ ($CDCl_3$): 2.39 - 2.47 (2H, m), 4.30 (2H, t), 4.82 (2H, t), 7.64 (1H, d), 8.21 (1H, d); *m/z* 198 $(M+H)^+$.

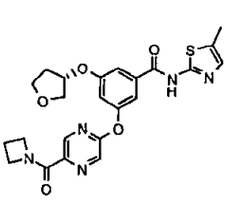
Ejemplo 43: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida

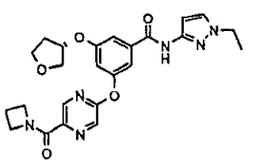
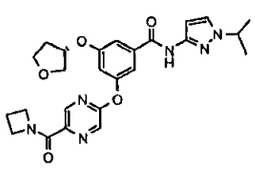
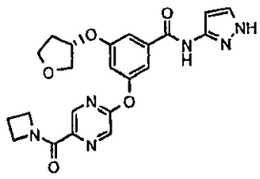
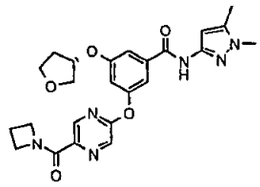


Ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico (200 mg, 0.52 mmol), HATU (475 mg, 1.25 mmol) y 2-amino-4-metiltiazol (119 mg, 1.04 mmol) se suspendieron en DMF (2 mL). A continuación se agregó DIPEA (0.220 mL, 1.26 mmol) y la mezcla de reacción se agitó a temperatura de la sala durante 16 horas. El DMF se retiró *in vacuo* y se agregó agua (15 mL). La mezcla se extrajo con acetato de etilo (3 x 20 mL) y los extractos combinados se lavaron con agua (15 mL), 1N ácido clorhídrico (10 mL), agua (10 mL), una solución acuosa saturada de bicarbonato de sodio (10 mL), salmuera (10 mL), se secó ($MgSO_4$), se filtró, y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 60-100% acetato de etilo en isohexano, para producir el compuesto deseado (70 mg).

^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.32 (s, 3H), 2.34 - 2.42 (m, 2H), 3.89 - 4.02 (m, 4H), 4.26 (t, 2H), 4.69 (t, 2H), 4.96 - 4.99 (m, 1H), 6.57 (d, 1H), 6.94 (t, 1H), 7.29 (t, 1H), 7.33 (t, 1H), 8.35 (d, 1H), 8.85 (d, 1H), 9.72 (s, 1H); *m/z* 482 $(M+H)^+$, 480 $(M-H)^-$.

Los siguientes compuestos se prepararon en una forma análoga de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico y el aminoheterociclo apropiado.

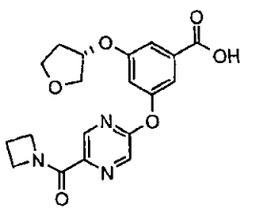
Ejemplo	Estructura	m/z	NMR
43a		482 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 2.38 (s, 3H), 3.88 -4.02 (m, 4H), 4.26 (t, 2H), 4.68 (t, 2H), 4.96 - 5.00 (m, 1H), 6.93 (t, 1H), 6.98 (s, 1H), 7.34 (t, 1H), 7.37 (t, 1H), 8.34 (d, 1H), 8.84 (d, 1H)

43b		479 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.46 (t, 3H), 2.13 -2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.88 -4.02 (m, 4H), 4.06 (q, 2H), 4.26 (t, 2H), 4.69 (t, 2H), 4.96 - 5.00 (m, 1H), 6.78 (d, 1H), 6.88 (t, 1H), 7.24 (t, 1H), 7.30 - 7.31 (m, 1H), 7.32 (d, 1H), 8.34 (d, 1H), 8.36 (s, 1H), 8.86 (d, 1H)
43c		493 $(M+H)^+$ 491 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 1.48 (d, 6H), 2.13 -2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.88 -4.02 (m, 4H), 4.26 (t, 2H), 4.36 (septete, 1H), 4.69 (t, 2H), 4.97 - 5.00 (m, 1H), 6.77 (d, 1H), 6.88 (t, 1H), 7.24 - 7.25 (m, 1H), 7.31 - 7.31 (m, 1H), 7.35 (d, 1H), 8.33 (d, 1H), 8.34 (s, 1H), 8.86 (d, 1H)
43d*		451 $(M+H)^+$ 449 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.88 - 4.02 (m, 4H), 4.26 (t, 2H), 4.69 (t, 2H), 4.96 - 5.00 (m, 1H), 6.84 (s, 1H), 6.87 (t, 1H), 7.28 (t, 1H), 7.31 (t, 1H), 7.46 (d, 1H), 8.36 (d, 1H), 8.83 (d, 1H), 9.45 (s, 1H), 10.05 (s, 1H)
43e		479 $(M+H)^+$ 477 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.11 - 2.24 (m, 2H), 2.26 (s, 3H), 2.33 - 2.41 (m, 2H), 3.61 (s, 3H), 3.87 - 4.00 (m, 4H), 4.25 (t, 2H), 4.68 (t, 2H), 4.93 - 4.97 (m, 1H), 6.58 (s, 1H), 6.86 (t, 1H), 7.24 (t, 1H), 7.28 (s, 1H), 8.32 (d, 1H), 8.84 (d, 1H), 8.85 (s, 1H)

* La reacción se llevó a cabo empleando 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato como el aminoheterociclo, el producto resultante se disolvió en acetonitrilo y se calentó en un reactor microondas a 150°C durante 5 - 10 minutos. Las mezclas se dejaron enfriar, luego se concentraron *in vacuo* para proporcionar los productos deseados. La preparación de 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se

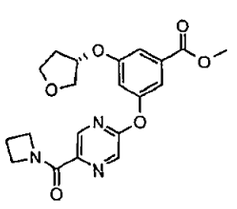
describió anteriormente. La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico se describe a continuación:

Ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)tetrahidrofuran-3-iloxi]benzoico



Metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato (7.02 mmol) se disolvió en THF (50 mL); se agregó 1N hidróxido de sodio (7.0 mL), seguido por agua (50 mL) y la solución resultante se agitó a temperatura de la sala durante 4 horas. Los orgánicos se retiraron *in vacuo*, la solución acuosa se filtró y se extrajo con acetato de etilo (30 mL). La capa acuosa se acidificó con 2N ácido clorhídrico, se extrajo con acetato de etilo (3 x 50 mL), y los extractos orgánicos se lavaron con agua (10 mL), salmuera (10 mL), luego se evaporaron a sequedad para producir el material deseado como una espuma blanca (2.33 g). ^{1}H NMR δ ($CDCl_3$): 2.14 - 2.30 (m, 2H), 2.34 - 2.42 (m, 2H), 3.89 - 3.94 (m, 2H), 3.97 - 4.02 (m, 2H), 4.28 (t, 2H), 4.69 (t, 2H), 4.97 - 5.00 (m, 1H), 6.94 (t, 1H), 7.48 (t, 2H), 8.34 (d, 1H), 8.85 (d, 1H); *m/z* 386 $(M+H)^+$, 384 $(M-H)^-$.

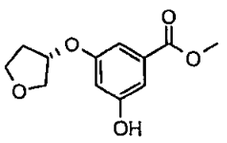
Metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato



Una solución de metil 3-hidroxi-5-[(3S)-tetrahidrofuran-3-iloxi]benzoato (2.5 g, 10.5 mmol), carbonato de potasio (2.9 g, 21.0 mmol) y 2-(azetidin-1-

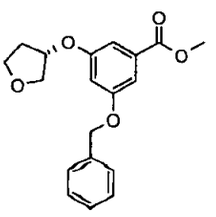
ilcarbonil)-5-cloropirazina (2.48 g, 12.6 mmol) en DMA (25 mL) se calentó a 120°C durante 2 horas. La solución se diluyó con acetato de etilo (150 mL), se lavó con agua (3 x 50 mL), salmuera (20 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo*. El residuo se purificó por cromatografía en sílice, eluyendo con 0-50% acetato de etilo en isohexano, para producir el compuesto deseado como un aceite incoloro (2.8 g). ^1H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.34 - 2.41 (m, 2H), 3.88 - 4.04 (m, 4H), 3.90 (s, 3H), 4.25 (t, 2H), 4.68 (t, 2H), 4.96 - 5.00 (m, 1H), 6.91 (t, 1H), 7.43 (d, 2H), 8.32 (d, 1H), 8.85 (d, 1H); *m/z* 386 $(M+H)^+$, 384 $(M-H)^-$.

Metil 3-hidroxi-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato



Metil 3-[(fenilmetil)oxi]-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato (25.0 g, 76.2 mmol) se disolvió en THF (150 mL) y etanol (150 mL). 10% Paladio sobre carbón (30 mg) se agregó y la mezcla se puso bajo una atmósfera de hidrógeno y se dejó agitando a temperatura de la sala hasta que la reacción se completó. El catalizador se retiró por filtración a través de tierra de diatomeas y el filtrado se concentró *in vacuo* para producir un aceite anaranjado, el cual se cristalizó luego de reposar. El sólido se extrajo completamente mediante filtración y se lavó con éter dietílico para producir el producto deseado como un sólido blanco (13.75 g).
^1H NMR δ ($CDCl_3$): 2.1-2.3 (2H, m), 3.9 (3H, s), 3.9-3.95 (2H, m), 3.97-4.05 (2H, m), 4.95 (1H, s), 5.6 (1), 6.6 (1H, t), 7.1 (1H, t), 7.13 (1H, t); *m/z* 237 $(M+H)^+$.

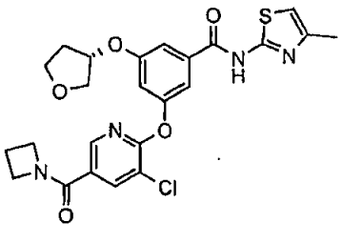
Metil 3-[(fenilmetil)oxi]-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato



Una mezcla de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (18.8 g, 72.75 mmol), (3*R*)-tetrahidrofuran-3-il 4-metilbencenosulfonato (18.5 g, 76.4 mmol) y carbonato de potasio (20.08 g, 145.5 mmol) en butironitrilo (250 mL) se calentó a 130°C durante 3 horas. El disolvente se retiró *in vacuo* y se agregó acetato de etilo. Los orgánicos se lavaron con agua (40 mL), 0.5M solución de hidróxido de sodio (40 mL), salmuera (40 mL), se secaron ($MgSO_4$), se filtraron y el disolvente se retiró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 0-5% metanol en DCM, para producir el compuesto deseado como un aceite incoloro (20.1 g). ^{1}H NMR δ ($CDCl_3$): 2.08 - 2.26 (m, 2H), 3.78 - 4.01 (m, 4H), 3.90 (s, 3H), 4.92 - 4.96 (m, 1H), 5.08 (s, 2H), 6.69 (t, 1H), 7.15 (t, 1H), 7.29 (t, 1H), 7.34 - 7.44 (m, 5H); *m/z* 327 $(M+H)^+$.

Las preparaciones de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato y (3*R*)-tetrahidrofuran-3-il 4-metilbencenosulfonato se describieron anteriormente.

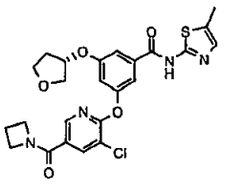
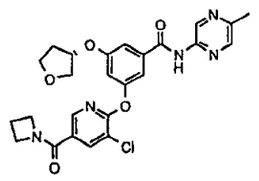
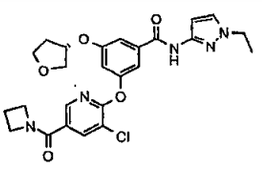
Ejemplo 44 : 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-*N*-(4-metil-1,3-tiazol-2-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida

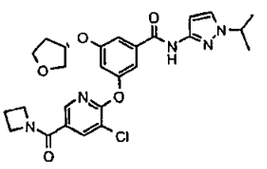
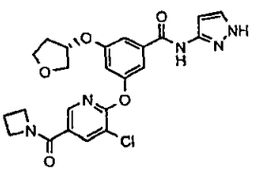


1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.70 mL, 0.53 mmol) se agregó a una solución de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico (200 mg, 0.48 mmol) en DCM (6 mL) y se agitó a temperatura de la sala durante 2 horas. 2-Amino-4-metiltiazol (110 mg, 0.96 mmol) y piridina (0.078 mL, 0.96 mmol) se agregaron y la reacción se agitó a temperatura de la sala durante 16 horas. El disolvente se retiró *in vacuo*, se agregó agua (20 mL) y la mezcla se extrajo con acetato de etilo (3 x 20 mL). Los extractos se combinaron y se lavó con 2N ácido clorhídrico (20 mL), solución de bicarbonato de sodio

acuoso saturado (20 mL), agua (20 mL), salmuera (20 mL), se secaron ($MgSO_4$), se filtraron, y se evaporaron *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 50-100% acetato de etilo en isohexano, para producir el compuesto deseado (78 mg). ^{1}H NMR δ ($CDCl_3$): 2.13 - 2.28 (m, 2H), 2.31 (s, 3H), 2.35 - 2.43 (m, 2H), 3.88 - 4.02 (m, 4H), 4.21 - 4.28 (m, 2H), 4.31 - 4.39 (m, 2H), 4.96 - 5.00 (m, 1H), 6.56 (d, 1H), 6.94 (t, 1H), 7.28 (t, 1H), 7.34 (t, 1H), 8.16 (d, 1H), 8.25 (d, 1H), 9.83 (s, 1H); *m/z* 515 $(M+H)^+$, 513 $(M-H)^-$.

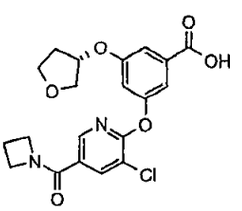
Los siguientes compuestos se prepararon en una forma análoga de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico y el aminoheterociclo apropiado.

Ejemplo	Estructura	m/z	NMR
44a		515 $(M+H)^+$ 513 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.34 -2.42 (m, 2H), 2.38 (s, 3H), 3.88 - 4.02 (m, 4H), 4.24 - 4.34 (m, 4H), 4.96 - 4.99 (m, 1H), 6.94 (t, 1H), 6.97 (d, 1H), 7.34 (t, 1H), 7.36 - 7.37 (m, 1H), 8.15 (d, 1H), 8.24 (d, 1H), 10.82 (s, 1H)
44b		510 $(M+H)^+$ 508 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.15 - 2.31 (m, 2H), 2.35 -2.43 (m, 2H), 2.56 (s, 3H), 3.89 - 4.03 (m, 4H), 4.20 - 4.39 (m, 4H), 4.99 - 5.03 (m, 1H), 6.93 (t, 1H), 7.29 (t, 1H), 7.35 (t, 1H), 8.14 (s, 1H), 8.16 (d, 1H), 8.26 (d, 1H), 8.36 (s, 1H), 9.54 (d, 1H)
44c		512 $(M+H)^+$ 510 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 1.46 (t, 3H), 2.14 - 2.30 (m, 2H), 2.35 - 2.43 (m, 2H), 3.88 - 4.02 (m, 4H), 4.06 (q, 2H), 4.20 - 4.28 (m, 2H), 4.31 - 4.39 (m, 2H), 4.97 - 5.01 (m, 1H), 6.78 (d, 1H), 6.89 (t, 1H), 7.23 (t, 1H), 7.30 - 7.31 (m, 1H), 7.32 (d, 1H), 8.16 (d, 1H), 8.25 (d, 1H), 8.37 (s, 1H)
44d		526	^{1}H NMR δ ($CDCl_3$): 1.48 (d, 6H), 2.14 -

		$(M+H)^+$ 524 $(M-H)^-$	2.29 (m, 2H), 2.35 - 2.43 (m, 2H), 3.88 - 4.02 (m, 4H), 4.20 - 4.28 (m, 2H), 4.30 - 4.40 (m, 2H), 4.36 (septete, 1H), 4.98 - 5.01 (m, 1H), 6.78 (d, 1H), 6.89 (t, 1H), 7.24 (t, 1H), 7.32 (t, 1H), 7.35 (d, 1H), 8.16 (d, 1H), 8.25 (d, 1H), 8.35 (s, 1H)
43e*		484 $(M+H)^+$ 482 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.29 (m, 2H), 2.34 - 2.42 (m, 2H), 3.87 - 4.02 (m, 4H), 4.20 - 4.28 (m, 2H), 4.29 - 4.37 (m, 2H), 4.97 - 5.00 (m, 1H), 6.85 (s, 1H), 6.88 (t, 1H), 7.29 - 7.30 (m, 1H), 7.31 - 7.31 (m, 1H), 7.44 (d, 1H), 8.15 (d, 1H), 8.21 (d, 1H), 9.76 (s, 1H), 10.17 (s, 1H)

* La reacción se llevó a cabo empleando 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato como el aminoheterociclo, el producto resultante se disolvió en acetonitrilo y se calentó en un reactor microondas a 150°C durante 5 - 10 minutos. Las mezclas se dejaron enfriar y se concentraron *in vacuo* para producir los productos deseados. La preparación de 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se describió anteriormente. La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico se describe a continuación:

Ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico

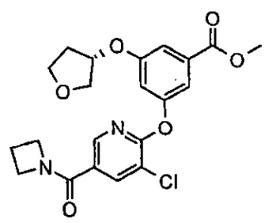


Metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato (3.75 g, 8.68 mmol) se disolvió en THF (40 mL); se agregó 1*N* hidróxido de sodio (8.68 mL, 8.68 mmol), seguido por agua (40 mL) y metanol (1 drop), y la solución resultante se agitó a temperatura de la sala durante 3 horas. Los orgánicos se retiraron *in vacuo*,

la solución acuosa se filtró y se extrajo con acetato de etilo (30 mL). La capa acuosa se acidificó con 2*N* ácido clorhídrico, se extrajo con acetato de etilo (3 x 50 mL), y los extractos orgánicos se lavaron con agua (10 mL), salmuera (10 mL), luego se evaporaron a sequedad para producir el material deseado como una espuma blanca (3.53 g).

^{1}H NMR δ ($CDCl_3$): 2.14 - 2.30 (m, 2H), 2.35 - 2.43 (m, 2H), 3.89 - 3.94 (m, 2H), 3.96 - 4.02 (m, 2H), 4.22 - 4.38 (m, 4H), 4.97 - 5.01 (m, 1H), 6.95 (t, 1H), 7.46 - 7.47 (m, 1H), 7.49 - 7.50 (m, 1H), 8.15 (d, 1H), 8.26 (d, 1H); *m/z* 419 $(M+H)^+$, 417 $(M-H)^-$.

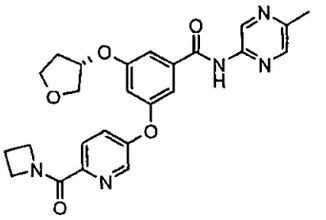
Metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato



Una solución de metil 3-hidroxi-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato (2.5 g, 10.5 mmol), carbonato de potasio (2.9 g, 21.0 mmol) y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (2.9 g, 12.6 mmol) en DMA (25 mL) se calentó a 120°C durante 5 horas. La solución se diluyó con acetato de etilo (150 mL), se lavó con agua (3 x 50 mL), salmuera (20 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo*. El residuo se purificó por cromatografía en sílice, eluyendo con 20-50% acetato de etilo en isohexano, para producir el compuesto deseado como un aceite incoloro (3.75 g). ^{1}H NMR δ ($CDCl_3$): 2.13 - 2.29 (m, 2H), 2.38 (quintete, 2H), 3.85 - 4.04 (m, 4H), 3.90 (s, 3H), 4.19 - 4.37 (m, 4H), 4.96 - 5.00 (m, 1H), 6.91 (t, 1H), 7.42 - 7.45 (m, 2H), 8.14 (d, 1H), 8.25 (d, 1H); *m/z* 433 $(M+H)^+$.

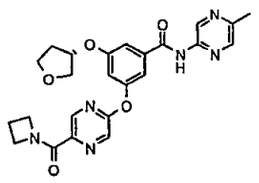
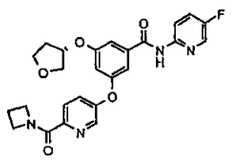
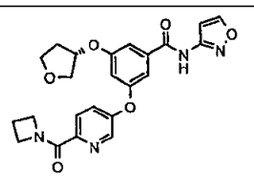
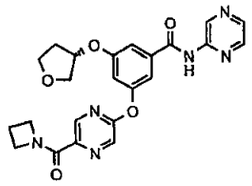
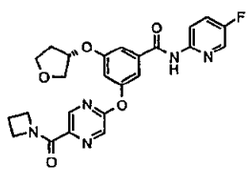
Las preparaciones de metil 3-hidroxi-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describieron anteriormente.

Ejemplo 45: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(5-metilpirazin-1-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.133 mL, 1.0 mmol) se agregó a una suspensión de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico (350 mg, 0.94 mmol) en DCM (10 mL) y se agitó a temperatura de la sala durante 30 minutos. 2-Amino-5-metilpirazina (196 mg, 1.82 mmol) y piridina (0.148 mL, 1.82 mmol) se agregaron y la reacción se agitó a temperatura de la sala durante 2 horas. El disolvente se retiró *in vacuo* y se agregó agua (30 mL). La mezcla se extrajo con acetato de etilo (3 x 20 mL), se lavó con 2N ácido clorhídrico (20 mL), agua (10 mL), solución de bicarbonato de sodio acuoso saturado (20 mL), agua (10 mL) y salmuera (20 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron *in vacuo*. El residuo se purificó por cromatografía, eluyendo con 0-10% metanol en DCM, para producir el producto deseado como un aceite incoloro (150 mg). ^{1}H NMR δ ($CDCl_3$): 2.12 - 2.18 (1H, m), 2.22 - 2.29 (1H, m), 2.31 - 2.40 (2H, m), 2.56 (3H, s), 3.89 - 4.03 (4H, m), 4.25 (2H, t), 4.71 (2H, t), 4.97 - 5.00 (1H, m), 6.76 (1H, t), 7.15 (1H, t), 7.25 (1H, d), 7.38 - 7.40 (1H, m), 8.12 (1H, s), 8.14 (1H, d), 8.32 (1H, s), 8.34 (1H, d), 9.52 (1H, d); *m/z* 476 $(M+H)^+$, 474 $(M-H)^-$.

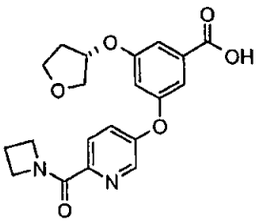
El siguiente compuesto se preparó en una forma análoga de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzoico o ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico y el aminoheterociclo apropiado.

Ejemplo	Estructura	m/z	NMR
45a		477 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.16-2.31 (m, 2H), 2.34 -2.42 (m, 2H), 2.56 (s, 3H), 3.89 - 4.02 (m, 4H), 4.26 (t, 2H), 4.69 (t, 2H), 4.98 - 5.02 (m, 1H), 6.92 (s, 1H), 7.30 (s, 1H), 7.35 (s, 1H), 8.15 (s, 1H), 8.36 (s, 2H), 8.86 (s, 1H), 9.54 (s, 1H)
45b		479 $(M+H)^+$ 477 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.31 (m, 2H), 2.32 -2.40 (m, 2H), 3.90 - 4.04 (m, 4H), 4.26 (t, 2H), 4.71 (t, 2H), 4.97 - 5.01 (m, 1H), 6.76 (t, 1H), 7.13 (t, 1H), 7.23 (t, 1H), 7.39 (dd, 1H), 7.48 -7.53 (m, 1H), 8.14 (d, 1H), 8.16 (d, 1H), 8.33 -8.38 (m, 2H), 8.47 (s, 1H)
45c		451 $(M+H)^+$ 449 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.13-2.31 (m, 2H), 2.32 -2.39 (m, 2H), 3.89 - 4.03 (m, 4H), 4.25 (t, 2H), 4.71 (t, 2H), 4.97 - 5.01 (m, 1H), 6.79 (t, 1H), 7.18 (d, 1H), 7.22 (t, 1H), 7.27 (t, 1H), 7.37 (dd, 1H), 8.11 (d, 1H), 8.28 (d, 1H), 8.33 (d, 1H), 9.47 (s, 1H)
45d		463 $(M+H)^+$ 461 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.15 - 2.32 (m, 2H), 2.35 -2.43 (m, 2H), 3.90 - 4.06 (m, 4H), 4.27 (t, 2H), 4.70 (t, 2H), 5.00 - 5.05 (m, 1H), 6.93 (t, 1H), 7.31 (t, 1H), 7.36 (t, 1H), 8.29 (t, 1H), 8.38 -8.38 (m, 1H), 8.40 - 8.41 (m, 1H), 8.46 (s, 1H), 8.86 (d, 1H), 9.68 (s, 1H)
45e		480 $(M+H)^+$ 478 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.15 - 2.31 (m, 2H), 2.35 -2.43 (m, 2H), 3.90 - 4.03 (m, 4H), 4.27 (t, 2H), 4.69 (t, 2H), 4.99 - 5.02 (m, 1H), 6.91 (t, 1H), 7.28 (t, 1H), 7.33 (t, 1H), 7.48 - 7.53 (m, 1H), 8.16 (d, 1H), 8.35 - 8.39 (m, 1H), 8.37 (d, 1H), 8.51 (s, 1H), 8.86 (d, 1H)

La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(3*S*)- tetrahidrofuran-3-iloxi]benzoico se describió anteriormente.

La preparación de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)- tetrahidrofuran-3-iloxi]benzoico se describe a continuación:

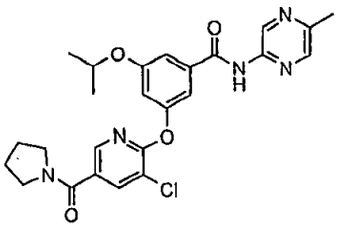
Ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-3-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico



Metil 3-hidroxi-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoato (875 mg, 3.68 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (1.06 g, 4.41 mmol), carbonato de cesio (3.59 g, 11.03 mmol), y bromotris(trifenilfosfina) cobre (0.69 g, 0.735 mmol) se agregaron juntos en DMA (16 mL) y se calentaron en un reactor microondas a 160°C durante 9 horas. La mezcla se tomó en agua (25 mL) y se lavó con acetato de etilo (2 x 20 mL). La capa acuosa se acidificó con 1N ácido clorhídrico (30 mL) y se extrajo con acetato de etilo (5 x 30 mL). El extracto orgánico combinado se lavó con agua (30 mL), salmuera (30 mL), se secó ($MgSO_4$), se filtró y se evaporó para producir un sólido marrón, el cual se trituró con éter dietílico para producir el compuesto deseado como un sólido color crema (820 mg). ^{1}H NMR δ (d_6-DMSO): 2.00 - 2.06 (m, 1H), 2.23 - 2.37 (m, 3H), 3.78 - 3.95 (m, 4H), 4.13 (t, 2H), 4.64 (t, 2H), 5.16 - 5.19 (m, 1H), 7.05 (t, 1H), 7.18 - 7.19 (m, 1H), 7.33 - 7.34 (m, 1H), 7.62 (dd, 1H), 8.04 (d, 1H), 8.46 (d, 1H); *m/z* 385 $(M+H)^+$, 383 $(M-H)^-$.

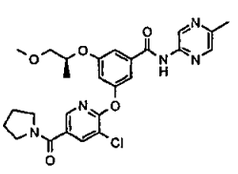
Las preparaciones de metil 3-hidroxi-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzoato y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describieron anteriormente.

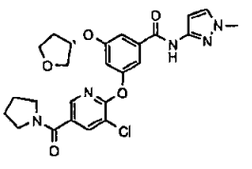
Ejemplo 46: 3-{[3-Cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il] oxi}-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida



Carbonato de cesio (782 mg, 2.4 mmol) se agregó a una solución de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida (230 mg, 0.8 mmol) y 2,3-dicloro-5-(pirrolidin-1-ilcarbonil)piridina (234 mg, 0.96 mmol) en acetonitrilo (5 mL) y la mezcla agitada se calentó en un reactor microondas a 120°C durante 2 horas. La mezcla se enfrió a temperatura de la sala y el acetonitrilo se evaporó *in vacuo*. El residuo se repartió en porciones entre agua (25 mL) y acetato de etilo (50 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 75% acetato de etilo en isohexano, para producir el compuesto deseado (290 mg). ^{1}H NMR δ ($CDCl_3$): 1.3 (d, 6H), 1.9 (m, 4H), 2.5 (s, 3H), 3.4-3.7 (m, 4H), 4.55 (m, 1H), 6.85 (d, 1H), 7.2 (d, 1H), 7.25 (d, 1H), 7.9 (d, 1H), 8.1 (dd, 1H), 8.2 (s, 1H), 8.35 (s, 1H) y 9.45 (s, 1H); *m/z* 496 $(M+H)^+$.

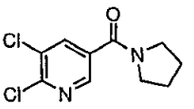
Los siguientes compuestos se prepararon en una forma análoga de 2,3-dicloro-5-(pirrolidin-1-ilcarbonil)piridina y 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida o 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzamida.

Ejemplo	Estructura	m/z	NMR
46a		526 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.3 (d, 3H), 1.9 (m, 4H), 2.5 (s, 3H), 3.3 (s, 3H), 3.4 - 3.6 (m, 6H), 4.55 (m, 1H), 6.9 (d, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 7.95 (d, 1H), 8.05 (s, 1H), 8.15 (d, 1H), 8.35 (s, 1H), 9.5 (s, 1H).
45b		512 $(M+H)^+$	1H NMR δ ($CDCl_3$): 1.8 - 1.95 (m, 4H), 2.1 (m, 2H), 3.45 (t, 2H), 3.6 (t, 2H), 3.7

			(s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.9 (m, 1H), 6.7 (d, 1H), 6.8 (d, 1H), 7.15 (d, 1H), 7.25 (d, 2H), 7.95 (d, 1H), 8.1 (d, 1H), 8.9 (s, 1H)

La preparación de 2,3-dicloro-5-(pirrolidin-1-ilcarbonil)piridina se describe a continuación:

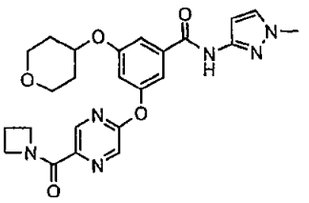
2,3-Dicloro-5-(pirrolidin-1-ilcarbonil)piridina



Cloruro de oxalilo (3.2 mL; 36.0 mmol) se agregó a una solución de ácido 5,6 dicloronicotínico (5.76 g; 30.0 mmol) y 4M cloruro de hidrógeno en dioxano (7.5 mL; 30.0 mmol) en DCM (50 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo*, el residuo se destiló bajo temperatura fija con tolueno (2 x 15 mL), luego se agregó a una solución de pirrolidina (3.0 mL; 36.0 mmol) y trietilamina (10.0 mL; 72 mmol) en DCM (150 mL). La mezcla se agitó a temperatura de la sala durante 6 horas, el DCM se evaporó *in vacuo*, el residuo se repartió en porciones entre agua (75 mL) y acetato de etilo (100 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el compuesto deseado, el cual se purificó posteriormente mediante cristalización de acetato de etilo e isohexano (6.88 g). ^{1}H NMR δ ($CDCl_3$): 1.9 (m, 4H), 3.4 (m, 2H), 3.6 (s, 3H), 7.9 (s, 1H) y 8.4 (s, 1H); *m/z* 245 $(M+H)^+$.

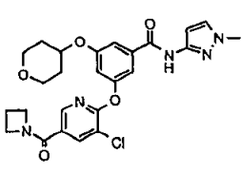
Las preparaciones de 3-hidroxi-5-[(1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida y 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida se describieron anteriormente.

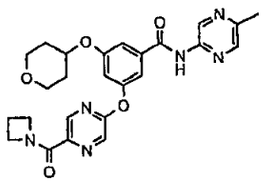
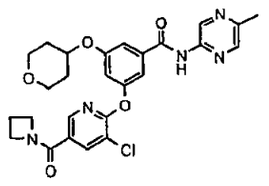
Ejemplo 47: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida



3-Hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi) benzamida (209 mg, 0.66 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (159 mg, 0.80 mmol) y carbonato de potasio (184 mg, 1.33 mmol) se disolvieron / se suspendieron en acetonitrilo (3.5 mL). La mezcla de reacción se calentó en un reactor microondas durante 4 horas a 120°C, luego se enfrió, se filtró y se redujo *in vacuo*. El producto crudo se purificó por cromatografía en sílice, eluyendo con 0-5% metanol en DCM, para proporcionar el producto requerido como una espuma blanca (39 mg). ^{1}H NMR δ (d_6-DMSO): 1.57 - 1.68 (m, 2H), 1.97 - 2.05 (m, 2H), 2.26 - 2.36 (m, 2H), 3.47 - 3.55 (m, 2H), 3.78 (s, 3H), 3.84 - 3.91 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.67 - 4.75 (m, 1H), 6.58 (d, 1H), 7.11 (t, 1H), 7.43 (t, 1H), 7.54 (t, 1H), 7.60 (d, 1H), 8.56 (d, 1H), 8.68 (d, 1H), 10.80 (s, 1H); *m/z* 479 $(M+H)^+$.

Los siguientes compuestos se elaboraron en una forma análoga de la 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida o la 3-hidroxi-*N*-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida y el heterociclo halogenado apropiado.

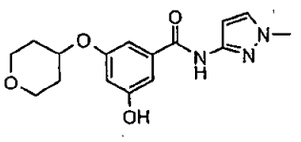
Ejemplo	Estructura	m/z	NMR
47a		512 $(M+H)^+$	^{1}H NMR 6 (d_6-DMSO): 1.57 -1.67 (m, 2H), 1.98 - 2.06 (m, 2H), 2.21 - 2.32 (m, 2H), 3.47 - 3.55 (m, 2H), 3.78 (s, 3H), 3.84 - 3.91 (m, 2H), 4.01-4.10 (m, 2H), 4.33 - 4.41 (m, 2H), 4.67 - 4.75 (m, 1H), 6.57 (d, 1H), 7.09 (t, 1H), 7.40 (t, 1H), 7.52 (t, 1H), 7.60 (d, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 10.79 (s, 1H)

47b		491 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.58 -1.68 (m, 2H), 1.99 - 2.06 (m, 2H), 2.26 - 2.35 (m, 2H), 2.49 (s, 3H), 3.47 - 3.55 (m, 2H), 3.84 - 3.91 (m, 2H), 4.10 (t, 2H), 4.57 (t, 2H), 4.69 - 4.77 (m, 1H), 7.18 (t, 1H), 7.49 (t, 1H), 7.58 (t, 1H), 8.36 (d, 1H), 8.57 (d, 1H), 8.68 (d, 1H), 9.25 (d, 1H), 10.98 (s, 1H)
47c		524 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.63 (m, 2H), 2.02 (m, 2H), 2.27 (m, 2H), 2.49 (s, 3H), 3.51 (m, 2H), 3.87 (m, 2H), 4.06 (t, 2H), 4.36 (t, 2H), 4.74 (m, 1H), 7.16 (t, 1H), 7.47 (t, 1H), 7.57 (t, 1H), 8.23 (d, 1H), 8.34 (d, 1H), 8.36 (m, 1H), 9.25 (d, 1H), 10.98 (s, 1H)

Las preparaciones de 2-(azetidin-1-ilcarbonil)-5-cloropirazina y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describieron anteriormente.

La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida se describe a continuación:

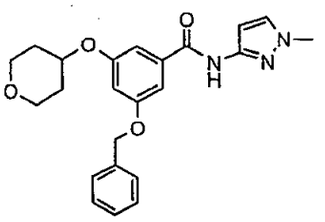
3-Hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2*H*-piran-4-iloxi) benzamida



N-(1-Metil-1*H*-pirazol-3-il)-3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida (1.85 g, 4.54 mmol) se disolvió en etanol (40 mL) y se agregó catalizador 10% paladio sobre carbón vegetal (97 mg) bajo argón. La reacción se agitó bajo una atmósfera de hidrógeno durante 16 horas, luego se filtró a través de Celite®, y el filtrado se concentró *in vacuo* para producir el compuesto deseado como un sólido marrón claro (1.30 g). ^{1}H NMR δ (d_6-DMSO): 1.54 - 1.65 (m, 2H), 1.94 - 2.03 (m, 2H), 3.44 - 3.54 (m, 2H), 3.78 (s, 3H), 3.83 - 3.90 (m, 2H), 4.56 - 4.65 (m, 1H), 6.51 (t, 1H),

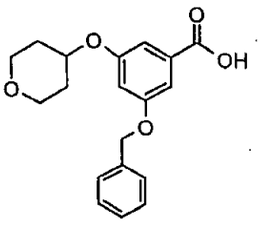
6.56 (d, 1H), 6.97 (t, 1H), 7.08 (t, 1H), 7.59 (d, 1H), 9.63 (s, 1H), 10.59 (s, 1H); *m/z* 318 $(M+H)^+$.

N-(1-Metil-1*H*-pirazol-3-il)-3-[(fenilmetil)oxil-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida



Ácido 3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzoico (3.14 g, 9.5 mmol), 1-metil-1*H*-pirazol-3-amina (1.85 g, 19.0 mmol) y HATU (4.70 g, 12.35 mmol) se disolvieron en DMF (12.5 mL), y se agregó DIPEA (3.31 mL, 19.0 mmol). La mezcla resultante se agitó a temperatura de la sala durante 20 horas. La mezcla se extinguió con agua (150 mL), se extrajo con acetato de etilo (2 x 75 mL), se lavó con salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con 0-50% acetato de etilo en isohexano, para producir el compuesto deseado como una goma amarillo pálido (1.85 g).

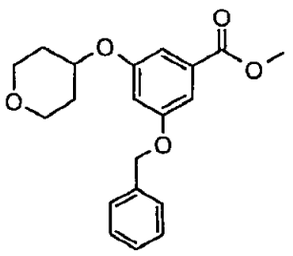
Ácido 3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzoico



Metil 3-[(fenilmetil)oxi]-5-(tetrahidro-2H-piran-4-iloxi)benzoato (9.00 g, 26.3 mmol) se disolvió en THF (120 mL), y se agregó metanol (30 mL) a una solución de monohidrato de hidróxido de litio (3.24 g, 78.9 mmol) en agua (60 mL). La solución bi-fásica se agitó a temperatura de la sala durante 3 horas hasta que se indicó la conversión completa por LCMS. Los orgánicos se retiraron *in vacuo* y se agregó agua (40 mL). El pH de la mezcla se ajustó a 7 mediante la adición de ácido clorhídrico, y el

precipitado resultante se filtró y se lavó con agua fría para producir el compuesto deseado como un sólido blanco (8.03 g). ^{1}H NMR δ (d_6-DMSO): 1.57 (m, 2H), 1.94 (m, 2H), 3.50 (m, 2H), 3.84 (m, 2H), 4.62 (m, 1H), 5.15 (s, 2H), 6.87 (t, 1H), 7.09 (m, 1H), 7.14 (m, 1H), 7.34 (t, 1H), 7.40 (t, 2H), 7.46 (d, 2H), 12.99 (s, 1H); *m/z* 327 $(M+H)^+$.

Metil 3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzoato

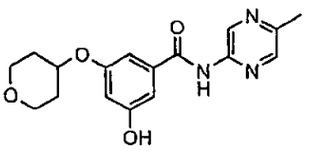


Metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (7.75 g, 30.0 mmol), tetrahidro-4*H*-piran-4-ol (4.28 mL, 45.0 mmol) y trifenilfosfina (11.8 g, 45.0 mmol) se agitaron bajo argón en THF (166 mL) y se enfriaron a 5°C en un baño helado. Se agregó DEAD (19.6 mL, 45.0 mmol) gota a gota a la mezcla, manteniendo la temperatura interna por debajo de 10°C. Se continuó la agitación durante 16 horas, luego la mezcla de reacción se redujo *in vacuo* y el residuo se redisolvió en acetato de etilo (60 mL) e isohexano (60 mL). El precipitado se retiró, el filtrado se concentró *in vacuo* y se purificó por cromatografía en sílice, eluyendo con 0-25% acetato de etilo en isohexano (se utilizó una pequeña cantidad de DCM para ayudar a cargar la columna), para producir el compuesto deseado como un aceite incoloro (9.0 g).

^{1}H NMR δ (d_6-DMSO): 1.58 (m, 2H), 1.94 (m, 2H), 3.49 (m, 2H), 3.84 (m, 5H), 4.65 (m, 1H), 5.16 (s, 2H), 6.92 (t, 1H), 7.10 (m, 1H), 7.15 (m, 1H), 7.34 (t, 1H), 7.40 (t, 2H), 7.46 (d, 2H); *m/z* 343 $(M+H)^+$.

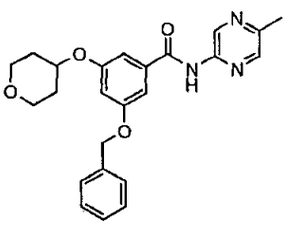
La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente. La preparación de 3-hidroxi-*N*-(5-metilpirazin-2-il)-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida se describe a continuación:

3-Hidroxi-*N*-(5-metilpirazin-2-il)-5-tetrahidro-2*H*-piran-4-iloxi) benzamida



N-(5-Metilpirazin-2-il)-3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida (1.70 g, 4.05 mmol) se disolvió en etanol (40 mL) y se agregó catalizador 10% paladio sobre carbón vegetal (86 mg) bajo argón. La reacción se agitó bajo una atmósfera de hidrógeno durante 4 días, luego se filtró y el filtrado se concentró *in vacuo* para producir el compuesto deseado como un sólido color crema (1.20 g). *m/z* 330 $(M+H)^+$.

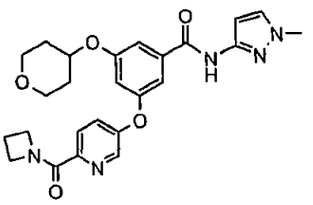
N-(5-Metilpirazin-2-il)-3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi) benzamida



Ácido 3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzoico (3.14 g, 9.5 mmol), 2-amino-5-metilpirazina (2.08 g, 19.0 mmol) y HATU (4.70 g, 12.35 mmol) se disolvieron en DMF (12.5 mL), y se agregó DIPEA (3.31 mL, 19.0 mmol). La mezcla resultante se agitó a temperatura de la sala durante 20 horas. La mezcla se extinguió con agua (150 mL) y se extrajo con acetato de etilo (2 x 75 mL), se lavó con salmuera, se secó ($MgSO_4$) y se concentró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con 0-50% acetato de etilo en isohexano, para producir el compuesto deseado como una goma amarillo pálido (1.70 g). *m/z* 420 $(M+H)^+$.

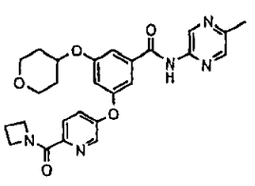
Las preparaciones de ácido 3-[(fenilmetil)oxi]-5-(tetrahidro-2*H*-piran-4-iloxi)benzoico y 2-amino-5 metilpirazina se describieron anteriormente.

Ejemplo 48: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida



3-Hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2*H*-piran-4-iloxi) benzamida (200 mg, 0.63 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (184 mg, 0.76 mmol), bromotris(trifenilfosfina)cobre (186 mg, 0.2 mmol) y carbonato de cesio (411 mg, 1.26 mmol) se disolvieron / se suspendieron en DMA (3.5 mL). La mezcla de reacción se calentó en un reactor microondas durante 1 hora a 200°C, luego se dejó enfriar, se filtró y se redujo *in vacuo*. Se agregó agua (25 mL) y el producto se extrajo con acetato de etilo (2 x 25 mL), los orgánicos se secaron ($MgSO_4$), luego se purificaron por cromatografía en sílice, eluyendo con 0-10% metanol en DCM, para producir el compuesto deseado como una espuma amarillo pálido (65 mg). ^{1}H NMR δ (de-DMSO): 1.57 - 1.67 (m, 2H), 1.97 - 2.05 (m, 2H), 2.23 - 2.34 (m, 2H), 3.51 (t, 2H), 3.78 (s, 3H), 3.83 - 3.90 (m, 2H), 4.08 (t, 2H), 4.59 (t, 2H), 4.69 - 4.76 (m, 1H), 6.56 (d, 1H), 7.00 (t, 1H), 7.29 (t, 1H), 7.49 (t, 1H), 7.54 - 7.58 (m, 1H), 7.60 (d, 1H), 8.00 (d, 1H), 8.41 (d, 1H), 10.83 (s, 1H); *m/z* 478 $(M+H)^+$.

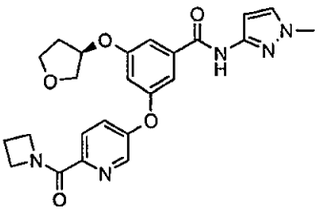
El siguiente compuesto se elaboró en una forma análoga de 2-(azetidin-1-ilcarbonil)-5-bromopiridina y 3-hidroxi-*N*-(5-metilpirazin-2-il)-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida.

Ejemplo	Estructura	m/z	NMR
48a		490 $(M+H)^+$	^{1}H NMR δ (d_6-DMSO): 1.62 (m, 2H), 2.01 (m, 2H), 2.28 (m, 2H), 2.48 (s, 3H), 3.50 (m, 2H), 3.86 (m, 2H), 4.07 (t, 2H), 4.59 (t, 2H), 4.75 (m, 1H), 7.08 (t, 1H), 7.49 (s, 1H), 7.53 (s, 1H), 7.56 (q, 1H),

			8.00 (d, 1H), 8.36 (s, 1H), 8.43 (d, 1H), 9.24 (d, 1H), 11.09 (s, 1H)

Las preparaciones de 2-(azetidin-1-ilcarbonil)-5-bromopiridina, 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-(tetrahidro-2*H*-piran-4-iloxi)benzamida y 3-hidroxi-*N*-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida se describieron anteriormente.

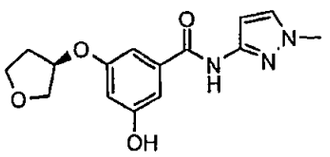
Ejemplo 49: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*R*)-tetrahidrofuran-3-iloxi]benzamida



Una mezcla de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*R*)-tetrahidrofuran-3-iloxi]benzamida (150 mg, 0.49 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (120 mg, 0.49 mmol), bromotris (trifenilfosfina)cobre (92 mg, 0.10 mmol) y carbonato de cesio (484 mg, 1.48 mmol) en acetonitrilo (7 mL) se agitó en un reactor microondas a 160°C durante 6 horas. El sólido se extrajo completamente por filtración, el disolvente se retiró *in vacuo* y se agregó acetato de etilo (50 mL) al residuo. La fase orgánica se lavó con agua (10 mL), salmuera (20 mL), se secó ($MgSO_4$), se filtró y el disolvente se retiró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en DCM, para producir el compuesto del título como un sólido blanco (86 mg). ^{1}H NMR δ ($CDCl_3$): 2.10 - 2.17 (m, 1H), 2.19 - 2.25 (m, 1H),2.32 - 2.38 (m, 2H), 3.76 (s, 3H), 3.87 - 3.92 (m, 1H), 3.95 - 4.01 (m, 3H), 4.24 (t, 2H), 4.71 (t, 2H), 4.97 (t, 1H), 6.73 (t, 1H), 6.81 (s, 1H), 7.11 (s, 1H), 7.24 (s, 1H), 7.27 - 7.30 (m, 1H), 7.36 - 7.39 (m, 1H), 8.12 (d, 1H), 8.31 (d, 1H), 8.72 (s, 1H); *m/z* 464 $(M+H)^+$.

La preparación de 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describió anteriormente. La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*R*)-tetrahidrofuran-3-iloxi]benzamida se describe a continuación:

3-Hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*R*)-tetrahidrofuran-3-iloxi] benzamida

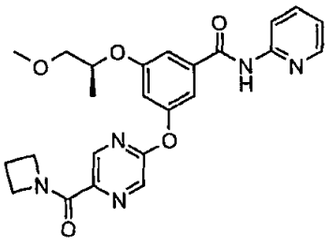


Una suspensión de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi]benzamida (450 mg, 1.39 mmol), (3*S*)-tetrahidrofuran-3-il 4-metilbencenosulfonato (507 mg, 2.09 mmol) y carbonato de potasio (481 mg, 3.48 mmol) en acetonitrilo (5 mL) se agitó en un reactor microondas a 160°C durante 3 horas. El disolvente se retiró *in vacuo* y se agregó acetato de etilo. Los orgánicos se lavaron con agua (40 mL), salmuera (40 mL), se secaron ($MgSO_4$), se filtraron y el disolvente se retiró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 0-100% acetato de etilo en isohexano, para producir *N*-(1-metil-1*H*-pirazol-3-il)-3-[(fenilmetil)oxi]-5-[(3*R*)-tetrahidrofuran-3-iloxi]benzamida como una espuma blanca. Ésta se disolvió en etanol (5 mL) y se agregó formiato de amonio (182 mg, 2.88 mmol) en una porción. La reacción se cubrió con argón y se agregó 10% paladio sobre carbón activado (30 mg). Esta mezcla se calentó en un reactor microondas a 140°C durante 10 minutos, el catalista se extrajo completamente mediante filtración, y los volátiles se retiraron *in vacuo* para producir el producto del título como un sólido blanco (305 mg). ^{1}H NMR δ (d_6-DMSO): 1.96 - 2.00 (m, 1H), 2.20 - 2.25 (m, 1H), 3.74 - 3.85 (m, 6H), 3.87 - 3.91 (m, 1H), 5.06 - 5.08 (m, 1H), 6.46 (t, 1H), 6.57 (d, 1H), 6.97 (s, 1H), 7.02 (s, 1H), 7.60 (d, 1H), 9.74 (s, 1H), 10.70 (s, 1H); *m/z* 304 $(M+H)^+$.

La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(fenilmetil)oxi] benzamida se describió anteriormente. (3*S*)-Tetrahidrofuran-3-il 4-

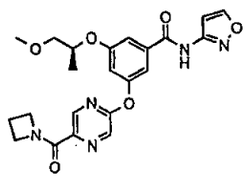
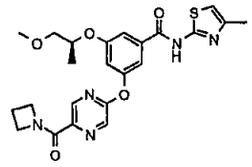
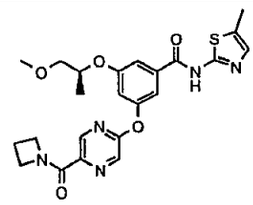
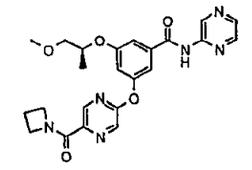
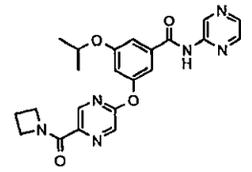
metilbencenosulfonato se preparó en una forma análoga a (3*R*)-tetrahidrofuran-3-il 4-metilbencenosulfonato, como se describe en el Ejemplo 25.

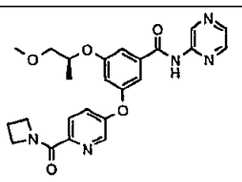
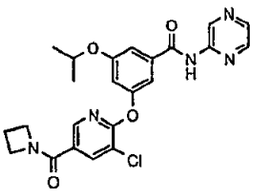
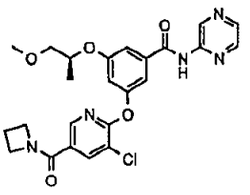
Ejemplo 50: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-piridin-2-ilbenzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.080 mL, 0.6 mmol) se agregó a una solución de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico (193 mg, 0.50 mmol) en DCM (10 mL) y se agitó a temperatura de la sala durante 30 minutos. 2-Aminopiridina (57 mg, 0.6 mmol) y piridina (0.082 mL, 1 mmol) se agregaron, y la reacción se agitó durante 16 horas más. El disolvente se retiró *in vacuo* y el residuo se tomó en acetato de etilo (50 mL). La fase orgánica se lavó con agua (2 x 20 mL), 1N ácido cítrico (10 mL), agua (10 mL), una solución acuosa de bicarbonato de sodio (10 mL) y salmuera (100 mL), luego se secó ($MgSO_4$), se filtró, y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 50-80% acetato de etilo en isohexano, para producir el compuesto deseado como una espuma blanca (42 mg). ^{1}H NMR δ ($CDCl_3$): 1.28 (d, 3H), 2.31 (quintete, 2H), 3.34 (s, 3H), 3.43 - 3.56 (m, 2H), 4.19 (t, 2H), 4.57 (q, 1H), 4.62 (t, 2H), 6.90 (s, 1H), 7.03 (t, 1H), 7.20 (s, 1H), 7.36 (s, 1H), 7.71 (t, 1H), 8.23 (d, 1H), 8.28 (s, 1H), 8.30 (d, 1H), 8.64 (s, 1H), 8.79 (s, 1H); *m/z* 464 $(M+H)^+$.

Los siguientes compuestos se prepararon en una forma análoga del ácido benzoico apropiado y el aminoheterociclo apropiado.

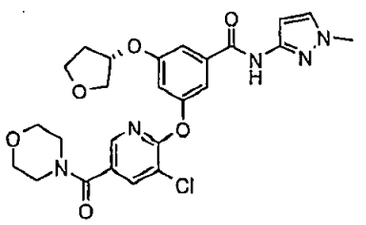
Ejemplo	Estructura	m/z	NMR
50a		454 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.26 - 2.38 (m, 2H), 3.34 (s, 3H), 3.42 - 3.57 (m, 2H), 4.19 (t, 2H), 4.51 - 4.70 (m, 3H), 6.92 (s, 1H), 7.12 (s, 1H), 7.27 (s, 1H), 7.36 (s, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.78 (s, 1H), 9.33 (s, 1H)
50b		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.22 (s, 3H), 2.27 - 2.39 (m, 2H), 3.33 (s, 3H), 3.41 - 3.57 (m, 2H), 4.19 (t, 2H), 4.50 - 4.58 (m, 1H), 4.62 (t, 2H), 6.50 (s, 1H), 6.92 (s, 1H), 7.23 (s, 1H), 7.35 (s, 1H), 8.27 (s, 1H), 8.78 (s, 1H)
50c		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.25 - 2.36 (m, 5H), 3.32 (s, 3H), 3.40 - 3.54 (m, 2H), 4.19 (t, 2H), 4.52 (q, 1H), 4.61 (t, 2H), 6.81 (s, 1H), 6.92 (s, 1H), 7.28 (s, 1H), 7.38 (s, 1H), 8.25 (s, 1H), 8.77 (s, 1H)
50d		465 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 3H), 2.32 (quin, 2H), 3.34 (s, 3H), 3.44 - 3.56 (m, 2H), 4.19 (t, 2H), 4.56 (q, 1H), 4.62 (t, 2H), 6.92 (s, 1H), 7.23 (s, 1H), 7.35 (s, 1H), 8.21 (s, 1H), 8.29 (s, 1H), 8.33 (s, 1H), 8.43 (s, 1H), 8.79 (s, 1H), 9.61 (s, 1H)
50e		435 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 6H), 2.32 (quin, 2H), 4.19 (t, 2H), 4.56 (quin, 1H), 4.62 (t, 2H), 6.85 (s, 1H), 7.20 (s, 1H), 7.30 (s, 1H), 8.21 (s, 1H), 8.29 (s, 1H), 8.33 (s, 1H), 8.40 (s, 1H), 8.80 (s, 1H), 9.61 (s, 1H)
50f		464 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.29 (quin, 2H), 3.34 (s, 3H), 3.43 - 3.55 (m, 2H), 4.18 (t, 2H), 4.56 (q, 1H), 4.64 (t, 2H), 6.78 (s, 1H), 7.09 (s, 1H), 7.26 (s,

			1H), 7.32 (d, 1H), 8.06 (d, 1H), 8.22 (s, 1H), 8.27 (s, 1H), 8.34 (s, 1H), 8.36 (s, 1H), 9.60 (s, 1H)
50g*		468 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.31 (d, 6H), 2.32 (quin, 2H), 4.17 (t, 2H), 4.29 (t, 2H), 4.57 (quin, 1H), 6.87 (s, 1H), 7.20 (s, 1H), 7.29 (s, 1H), 8.10 (s, 1H), 8.19 (s, 1H), 8.21 (s, 1H), 8.32 (s, 1H), 8.42 (s, 1H), 9.62 (s, 1H)
50h		498 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.29 (d, 3H), 2.32 (quin, 2H), 3.35 (s, 3H), 3.43 - 3.57 (m, 2H), 4.17 (t, 2H), 4.29 (t, 2H), 4.57 (q, 1H), 6.93 (s, 1H), 7.24 (s, 1H), 7.35 (s, 1H), 8.10 (s, 1H), 8.19 (s, 1H), 8.21 (s, 1H), 8.32 (s, 1H), 8.42 (s, 1H), 9.62 (s, 1H)

* La muestra aislada se contaminó con aproximadamente 15% de una impureza desconocida, luego de la cromatografía inicial.

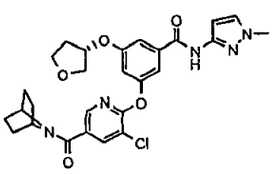
Las preparaciones de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]benzoico, ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil] oxi}benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]benzoico, y ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}benzoico se describieron anteriormente.

Ejemplo 51: 3-{[3-Cloro-5-(morfolin-4-ilcarbonil)piridin-2-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida



Carbonato de cesio (489 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzamida (152 mg, 0.5 mmol) y 4-[(5,6-dicloropiridin-3-il)carbonil] morfolina (143 mg, 0.55 mmol) en acetonitrilo (5 mL), y la mezcla se calentó a 120°C en un reactor microondas durante 2 horas. El acetonitrilo se evaporó *in vacuo* y el residuo se repartió en porciones entre agua (25 mL) y acetato de etilo (50 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con acetato de etilo, para producir el compuesto deseado (203 mg). ^{1}H NMR δ ($CDCl_3$): 2.05 - 2.2 (m, 2H), 3.4 - 3.7 (m, 8H), 3.7 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.9 (m, 1H), 6.7 (d, 1H), 6.8 (d, 1H), 7.15 (d, 1H), 7.25 (d, 2H), 7.85 (d, 1H), 8.0 (d, 1H), 8.95 (s, 1H); *m/z* 512 $(M+H)^+$.

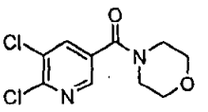
El siguiente compuesto se preparó en una forma análoga de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida y 7-[(5,6-dicloropiridin-3-il)carbonil]-7-azabiciclo [2.2.1]heptano

Ejemplo	Estructura	m/z	NMR
51a		538 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.5 (m, 4H), 1.7-1.9 (m, 4H), 2.05 - 2.2 (m, 2H), 3.7 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.1 (m, 1H), 4.7 (m, 1H), 4.9 (m, 1H), 6.75 (d, 1H), 6.85 (d, 1H), 7.2 (d, 1H), 7.25 (d, 2H), 8.0 (d, 1H), 8.2 (d, 1H) y 9.0 (s, 1H).

La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida se describió anteriormente.

La preparación de 4-[(5,6-dicloropiridin-3-il)carbonil]morfolina se describe a continuación:

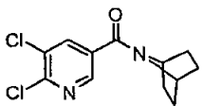
4-[(5,6-Dicloropiridin-3-il)carbonil]morfolina



Cloruro de oxalilo (3.2 mL; 36.0 mmol) se agregó a una solución de ácido 5,6 dicloronicotínico (5.76 g; 30.0 mmol) y 4M cloruro de hidrógeno en dioxano (7.5 mL; 30 mmol) en DCM (50 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo*, el residuo se destiló a temperatura fija con tolueno (2 x 15 mL) y se agregó a una solución de morfolina (3.1 mL; 36.0 mmol) y trietilamina (10.0 mL; 72 mmol) en DCM (150 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo*, y el residuo se repartió en porciones entre agua (75 mL) y acetato de etilo (100 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el compuesto deseado (7.1 g). ^{1}H NMR δ ($CDCl_3$): 3.3 - 3.8 (br, 8H), 7.8 (s, 1H), 8.25 (s, 1H); *m/z* 261 $(M+H)^+$.

La preparación de 7-[(5,6-dicloropiridin-3-il)carbonil]-7-azabiciclo[2.2.1] heptano se describe a continuación:

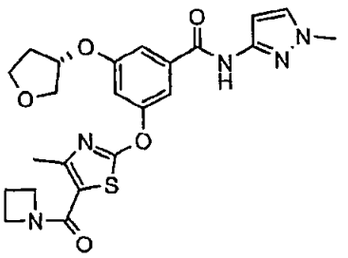
7-[(5,6-Dicloropiridin-3-il)carbonil]-7-azabiciclo[2.2.1]heptano



Cloruro de oxalilo (3.2 mL; 36.0 mmol) se agregó a una solución de ácido 5,6 dicloronicotínico (5.76 g, 30.0 mmol) y 4M cloruro de hidrógeno en dioxano (7.5 mL; 30.0 mmol) en DCM (50 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in vacuo*, el residuo se destiló a temperatura fija con tolueno (2 x 15 mL) y se agregó a una solución de clorhidrato de 7-azabiciclo[2.2.1]heptano (4.75 g; 36.0 mmol) y trietilamina (15.1 mL; 108 mmol) en DCM (150 mL). La mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se evaporó *in*

vacuo y el residuo se repartió en porciones entre agua (75 mL) y acetato de etilo (150 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó para producir un sólido, el cual se cristalizó de acetato de etilo para producir el compuesto deseado (5.45 g). ^{1}H NMR δ ($CDCl_3$): 1.5 (m, 4H), 1.85 (m, 4H), 4.0 (br, 1H), 4.65 (br, 1H), 7.9 (s, 1H), 8.4 (s, 1H); *m/z* 271 $(M+H)^+$.

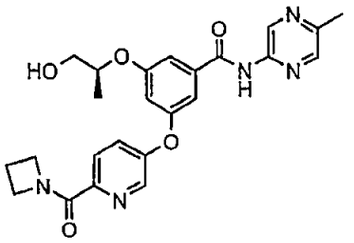
Ejemplo 52: 3-{[5-(Azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida



Carbonato de cesio (489 mg, 1.5 mmol) se agregó a una solución de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzamida (152 mg, 0.5 mmol) y 5-(azetidin-1-ilcarbonil)-2-bromo-4-metil-1,3-tiazol (144 mg, 0.55 mmol) en acetonitrilo (5 mL), y la mezcla agitada se calentó a 120°C en un reactor microondas durante 2 horas. La mezcla se dejó enfriar, el acetonitrilo se evaporó *in vacuo,* y el residuo se repartió en porciones entre agua (25 mL) y acetato de etilo (50 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con acetato de etilo, para producir el compuesto deseado como un sólido, el cual se cristalizó posteriormente de una mezcla de acetato de etilo / isohexano (122 mg). ^{1}H NMR δ ($CDCl_3$): 2.0 - 2.15 (m, 2H), 2.2 - 2.3 (m, 2H), 2.5 (s, 3H), 3.75 (s, 3H), 3.85 (m, 2H), 3.95 (d, 2H), 4.1 -4.3 (m, 4H), 4.9 (m, 1H), 6.75 (d, 1H), 6.95 (d, 1H), 7.25 (d, 2H), 7.3 (d, 1H) y 8.8 (s, 1H); *m/z* 484 $(M+H)^+$.

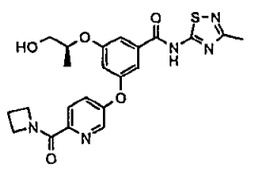
Las preparaciones de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida y 5-(azetidin-1-ilcarbonil)-2-bromo-4-metil-1,3-tiazol se describieron anteriormente.

Ejemplo 53: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida



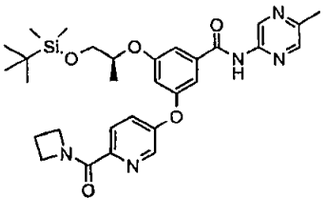
1M de ácido clorhídrico (5 mL) se agregó a una solución de 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida (82 mg, 0.14 mmol) en metanol (5 mL) y se agitó a temperatura de la sala durante 1 hora. El metanol se retiró *in vacuo* y el residuo se tomó a pH6, se extrajo en acetato de etilo (3 x 50 mL), y los orgánicos combinados se lavaron con salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo*. El aceite amarillo crudo se cromatografió en sílice, eluyendo con 0-5% metanol en acetato de etilo, para producir el compuesto deseado como una espuma blanca (36 mg). El compuesto pudo cristalizarse de una mezcla de *terc*-butilmetil éter y metanol. ^{1}H NMR δ ($CDCl_3$): 1.24 (d, 3H), 1.81 (s, 1H), 2.28 (quintete, 2H), 2.48 (s, 3H), 3.67 - 3.72 (m, 2H), 4.17 (t, 2H), 4.47 - 4.54 (m, 1H), 4.63 (t, 2H), 6.73 (t, 1H), 7.09 (t, 1H), 7.25 (t, 1H), 7.27 - 7.30 (m, 1H), 8.01 - 8.06 (m, 2H), 8.24 (d, 1H), 8.58 (s, 1H), 9.44 (d, 1H); *m/z* 464 $(M+H)^+$.

El siguiente compuesto se sintetizó en una forma análoga de 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(3-metil-1,2,4-tiadiazol-5-il)benzamida.

Ejemplo	Estructura	m/z	NMR
53a		470 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.22 (d, 3H), 2.28 (quin, 2H), 2.40 (s, 3H), 3.00 (s, 1H), 3.70 (d, 2H), 4.16 (t, 2H), 4.51 (sextet, 1H), 4.64 (t, 2H), 6.74 (t, 1H), 7.20 - 7.27 (m, 3H), 7.97 (d, 1H), 8.23 (d, 1H), 11.55 (s, 1H)

La preparación de 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida se describe a continuación.

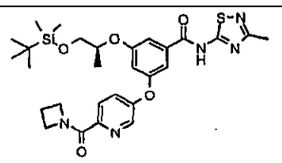
3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.11 mL, 0.80 mmol) se agregó a una solución de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico (0.3 g, 0.62 mmol) en DCM (10 mL) y se agitó durante 1 hora. Se agregaron 2-amino-5-metilpirazina (135 mg, 1.23 mmol), luego piridina (0.1 mL, 1.23 mmol), y la mezcla se agitó durante 30 minutos más antes de reducirse *in vacuo* y se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa acuosa se extrajo posteriormente en acetato de etilo (50 mL) y los orgánicos combinados se lavaron con agua (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo*. El aceite crudo se cromatografió en sílice, eluyendo con 40-100% acetato de etilo en isohexano, para producir el compuesto deseado como un aceite incoloro (82 mg). ^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.28 (d, 3H), 2.32 (quintete, 2H), 2.53 (s, 3H), 3.64 - 3.77 (m, 2H), 4.22 (t, 2H), 4.47 - 4.51 (m, 1H), 4.68 (t, 2H), 6.81 (t, 1H), 7.10 (t, 1H), 7.27 (t, 1H),

7.33 - 7.35 (m, 1H), 8.08 - 8.11 (m, 2H), 8.30 (d, 1H), 8.37 (s, 1H), 9.50 (d, 1H); *m/z* 578 $(M+H)^+$.

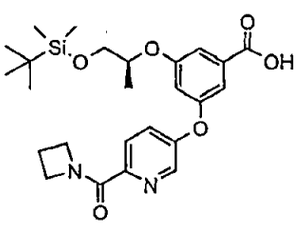
3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(3-metil-1,2,4-tiadiazol-5-il) benzamida se preparó en una forma análoga de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico.

Estructura	m/z
	584 $(M+H)^+$

La preparación de 2-amino-5-metilpirazina se describió anteriormente.

La preparación de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico se describe a continuación.

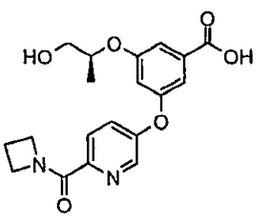
Ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico



terc-Butildimetilsilil cloruro (1.11 g, 7.36 mmol) se agregó a una mezcla de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}benzoico (1.37g, 3.68 mmol) y 1,8-diazabiciclo(5,4,0)undec-7-eno (1.11 mL, 7.36 mmol) en acetonitrilo (20 mL), y se agitó a temperatura de la sala durante 24 horas. El disolvente se retiró *in vacuo* y se agregó agua (80 mL) al aceite resultante. La mezcla se ajustó a pH 10 con solución 1M de bicarbonato de sodio, luego se lavó con éter (80 mL) para

retirar las impurezas. La capa acuosa se ajustó a pH 3 con 1M ácido cítrico y se extrajo en acetato de etilo (2 x 100 mL), y los orgánicos combinados se lavaron con salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo*. El material crudo se cromatografió en un cartucho Isolute NH2, eluyendo con metanol, luego amoníaco en metanol, para producir una espuma color crema. Este material se trituró posteriormente con acetato de etilo para producir el compuesto deseado como una espuma color crema (1.0 g). ^{1}H NMR δ ($CDCl_3$): 0.01 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.27 (d, 3H), 2.26 - 2.35 (m, 2H), 3.58 - 3.79 (m, 2H), 4.15 - 4.25 (m, 2H), 4.43 - 4.49 (m, 1H), 4.60 - 4.69 (m, 2H), 6.77 - 6.82 (m, 1H), 7.28 (m, 2H), 7.42 - 7.44 (m, 1H), 8.02 - 8.07 (m, 1H), 8.27 - 8.29 (m, 1H); *m/z* 487 $(M+H)^+$.

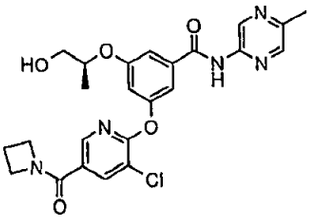
Ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}benzoico



Una mezcla de metil 3-hidroxi-5-[(1*S*)-2-hidroxi-1-metiletoxi]benzoato (2.35 g, 10.39 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (2.51 g, 10.39 mmol), carbonato de cesio (10.16 g, 31.16 mmol) y bromotris (trifenilfosfina)cobre (1.93 g, 2.08 mmol) en DMA (20 mL) se agitó en un reactor microondas a 160°C durante 8 horas. La mezcla se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa acuosa se acidificó con 1M ácido cítrico y se extrajo en acetato de etilo (2 x 100 mL), se lavó con salmuera, se secó ($MgSO_4$), y el disolvente se retiró *in vacuo*. El aceite crudo se cromatografió en un cartucho Isolute NH2, eluyendo con metanol, luego amoníaco en metanol, para producir el material deseado como una espuma color crema (1.37 g). *m/z* 373 $(M+H)^+$.

Las preparaciones de metil 3-hidroxi-5-[(1*S*)-2-hidroxi-1-metiletoxi]benzoato y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describieron anteriormente.

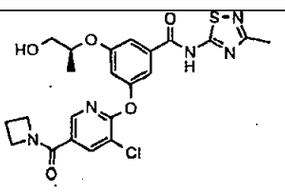
Ejemplo 54: 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida

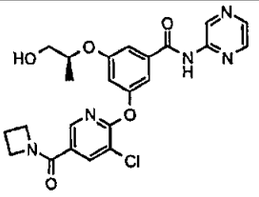
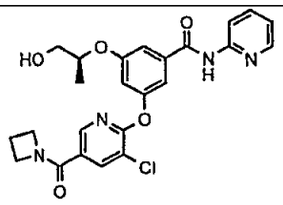


1M ácido clorhídrico (10 mL) se agregó a una solución de 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida (180 mg, 0.29 mmol) en metanol (10 mL) y se agitó a temperatura de la sala durante 1 hora. El metanol se retiró *in vacuo* y el residuo se ajustó a pH 6, luego se extrajo en acetato de etilo (3 x 50 mL). Los orgánicos combinados se lavaron con salmuera (50 mL), se secaron ($MgSO_4$), y se redujeron *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-5% metanol en acetato de etilo, para producir el compuesto deseado como una espuma blanca (134 mg). El compuesto se cristalizó de acetato de etilo y metanol.

^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.40 (quintete, 2H), 2.56 (s, 3H), 3.76 - 3.81 (m, 2H), 4.25 (t, 2H), 4.38 (t, 2H), 4.57 - 4.64 (m, 1H), 6.98 (t, 1H), 7.31 (t, 1H), 7.42 (t, 1H), 8.14 (s, 1H), 8.17 (d, 1H), 8.26 (d, 1H), 8.64 (s, 1H), 9.55 (s, 1H); *m/z* 498 $(M+H)^+$.

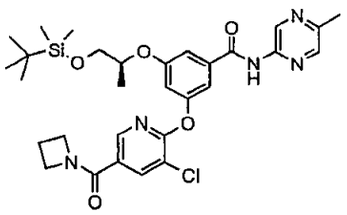
Los siguientes compuestos se prepararon en una forma análoga:

Ejemplo	Estructura	m/z	NMR
54a		504 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.30 (d, 3H), 2.40 (quin, 2H), 2.47 (s, 3H), 3.23 (s, 1H), 3.78 - 3.79 (m, 2H), 4.25 (t, 2H), 4.38 (t, 2H), 4.58 (sextet, 1H), 6.97 (t, 1H),

			7.39 - 7.40 (m, 2H), 8.15 (d, 1H), 8.22 (d, 1H), 11.68 (s, 1H)
54b		484 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.02 (t, 1H), 2.33 (quin, 2H), 3.70 - 3.73 (m, 2H), 4.17 (t, 2H), 4.30 (t, 2H), 4.52 - 4.56 (m, 1H), 6.93 (t, 1H), 7.24 (t, 1H), 7.35 (t, 1H), 8.10 (d, 1H), 8.19 (d, 1H), 8.21 - 8.22 (m, 1H), 8.33 (d, 1H), 8.43 (s, 1H), 9.61 (d, 1H)
54c		483 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.17 (t, 1H), 2.32 (quin, 2H), 3.67 - 3.74 (m, 2H), 4.17 (t, 2H), 4.30 (t, 2H), 4.49 - 4.56 (m, 1H), 6.89 (t, 1H), 7.00 - 7.03 (m, 1H), 7.23 (t, 1H), 7.34 (t, 1H), 7.67 - 7.71 (m, 1H), 8.10 (d, 1H), 8.18 (d, 1H), 8.22 - 8.23 (m, 1H), 8.28 (d, 1H), 8.54 (s, 1H)

La preparación de 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida se describe a continuación.

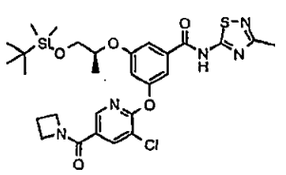
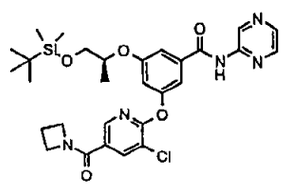
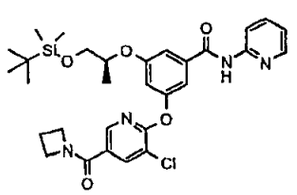
3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il) benzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.1 mL, 0.75 mmol) se agregó a una solución de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico (0.3 g, 0.58 mmol) en DCM (10 mL) y se agitó durante 1 hora. Se agregaron 2-amino-5-metilpirazina (126 mg, 1.15 mmol), luego piridina (0.094 mL, 1.15

mmol), y la mezcla se agitó durante 30 minutos más antes de reducirse *in vacuo* y se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa acuosa se extrajo posteriormente en acetato de etilo (50 mL) y los orgánicos combinados se lavaron con agua (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), y se redujeron *in vacuo*. El aceite crudo se cromatografió en sílice, eluyendo con 40-100% acetato de etilo en isohexano, para producir el compuesto del título como un aceite (180 mg). ^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.82 (s, 9H), 1.28 (d, 3H), 2.35 (quintete, 2H), 2.51 (s, 3H), 3.63 - 3.78 (m, 2H), 4.19 (t, 2H), 4.32 (t, 2H), 4.47 - 4.51 (m, 1H), 6.95 (t, 1H), 7.23 - 7.24 (m, 1H), 7.35 (t, 1H), 8.08 (s, 1H), 8.12 (d, 1H), 8.21 (d, 1H), 8.45 (s, 1H), 9.51 (d, 1H); *m/z* 612 $(M+H)^+$.

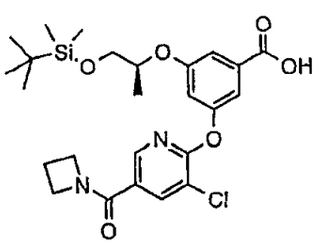
Los siguientes intermedios empleados en la preparación de **Ejemplos 54a-c** se prepararon en una forma análoga.

Estructura	m/z	NMR
	618 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.37 (d, 3H), 2.30 - 2.38 (m, 5H), 3.61 - 3.79 (m, 2H), 4.19 (t, 2H), 4.30 (t, 2H), 4.41 - 4.47 (m, 1H), 6.84 -6.86 (m, 1H), 7.62 - 7.62 (m, 1H), 7.72 - 7.73 (m, 1H), 8.10 - 8.11 (m, 1H), 8.19 - 8.20 (m, 1H), 9.89 (s, 1H)
	598 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.29 (d, 3H), 2.35 (quin, 2H), 3.64 - 3.79 (m, 2H), 4.19 (t, 2H), 4.32 (t, 2H), 4.47 - 4.51 (m, 1H), 6.96 (s, 1H), 7.25 (s, 1H), 7.36 (s, 1H), 8.12 (d, 1H), 8.21 (d, 1H), 8.23 (s, 1H), 8.34 (d, 1H), 8.52 (s, 1H), 9.64 (s, 1H)
	597 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.84 (s, 9H), 1.28 (d, 3H), 2.35 (quin, 2H), 3.63 - 3.78 (m, 2H), 4.19 (t, 2H), 4.32 (t, 2H), 4.46 - 4.50 (m, 1H), 6.93 (t, 1H), 7.01 - 7.05 (m, 1H), 7.23 - 7.23 (m, 1H), 7.34 (t, 1H), 7.69 - 7.73 (m, 1H), 8.12 (d, 1H), 8.21 (d, 1H), 8.24 (d, 1H),

		8.31 (d, 1H), 8.56 (s, 1H)

La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico se describe a continuación.

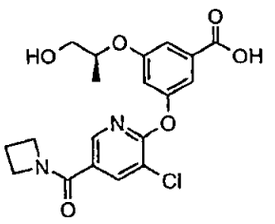
Ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]benzoico



terc-Butildimetilsilil cloruro (2.78 g, 18.4 mmol) se agregó a una mezcla de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}benzoico (3.74 g, 9.19 mmol) y 1,8-diazabiciclo(5,4,0)undec-7-eno (2.75 mL, 7.36 mmol) en acetonitrilo (40 mL) y se agitó a temperatura de la sala durante 24 horas. El disolvente se retiró *in vacuo* y se agregó agua (80 mL) al aceite resultante. La mezcla se ajustó a pH 10 con una solución 1M de bicarbonato de sodio y se lavó con éter para eliminar posibles impurezas. La capa acuosa se ajustó a pH3 con 1M ácido cítrico y se extrajo en acetato de etilo (2 x 100 mL). Los orgánicos combinados se lavaron con salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo* para producir el compuesto deseado como una espuma blanca (2.9 g).

^{1}H NMR δ ($CDCl_3$): 0.00 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.28 (d, 3H), 2.35 (quintete, 2H), 3.62 - 3.78 (m, 2H), 4.21 (t, 1H), 4.32 (t, 1H), 4.43 - 4.50 (m, 1H), 6.95 - 6.98 (m, 1H), 7.42 - 7.45 (m, 1H), 7.50 - 7.53 (m, 1H), 8.12 (d, 1H), 8.22 (d, 1H); *m/z* 521 $(M+H)^+$.

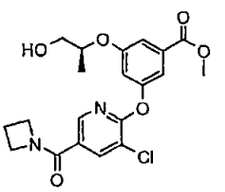
Ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}benzoico



Monohidrato de hidróxido de litio (529 mg, 12.59 mmol) en agua (25 mL) se agregó a una solución de metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}benzoato (5.3 g, 12.6 mmol) en THF (50 mL) y se agitó a temperatura de la sala durante 3 horas. El THF se retiró *in vacuo* y la capa acuosa se lavó con acetato de etilo (50 mL) para eliminar posibles impurezas. La capa acuosa se acidificó y se extrajo en acetato de etilo (2 x 50 mL), y los orgánicos se lavaron con salmuera, se secaron ($MgSO_4$), y se concentraron *in vacuo* para producir el compuesto deseado como una espuma blanca (3.74 g).

^{1}H NMR δ ($CDCl_3$): 1.24 (d, 3H), 2.31 (quintete, 2H), 3.65 - 3.72 (m, 2H), 4.17 (t, 2H), 4.29 (t, 2H), 4.47 - 4.54 (m, 1H), 6.93 (t, 1H), 7.40 (s, 1H), 7.46 (s, 1H), 8.08 (d, 1H), 8.19 (d, 1H); *m/z* 407 $(M+H)^+$.

Metil-3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}benzoato



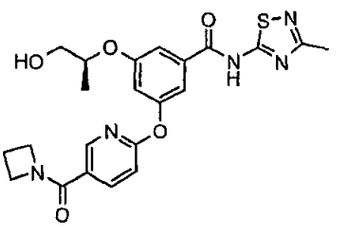
Una mezcla de metil 3-hidroxi-5-[(1*S*)-2-hidroxi-1-metiletoxi]benzoato (2.35 g, 10.39 mmol), 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (2.41 g, 10.39 mmol) y carbonato de potasio (2.87 g, 20.8 mmol) en acetonitrilo (20 mL) se agitó en un reactor microondas a 160°C durante 6 horas. El disolvente se retiró *in vacuo* y el residuo se repartió en porciones entre acetato de etilo (50 mL) y agua (50 mL). La capa orgánica se lavó con salmuera (50 mL), se secó ($MgSO_4$), y el disolvente se retiró *in vacuo*. El aceite crudo se cromatografió en sílice, eluyendo con 30-100% acetato de

etilo en isohexano, para producir el compuesto deseado as un aceite amarillo (5.3 g).

^{1}H NMR δ ($CDCl_3$): 1.24 (d, 3H), 1.94 (t, 1H), 2.32 (quintete, 2H), 3.65 - 3.72 (m, 2H), 3.83 (s, 3H), 4.16 (t, 2H), 4.28 (t, 2H), 4.47 - 4.54 (m, 1H), 6.90 (t, 1H), 7.37 - 7.38 (m, 1H), 7.43 - 7.45 (m, 1H), 8.08 (d, 1H), 8.18 (d, 1H); *m/z* 4.21 $(M+H)^+$.

Las preparaciones de metil 3-hidroxi-5-[(1*S*)-2-hidroxi-1-metiletoxi]benzoato y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina se describieron anteriormente.

Ejemplo 55: 3-{[5-(Azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(3-metil-1,2,4-tiadiazol-5-il)benzamida



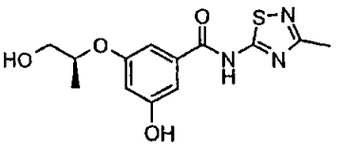
Una mezcla de 3-hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(3-metil-1,2,4-tiadiazol-5-il)benzamida (237 mg, 0.77 mmol), 5-(azetidin-1-ilcarbonil)-2-cloropiridina (151 mg, 0.77 mmol) y carbonato de potasio (213 mg, 1.54 mmol) en acetonitrilo (5 mL) se agitó en un reactor microondas a 140°C durante 5 horas y a 160°C durante 10 horas. La mezcla se redujo *in vacuo* y se agregó acetato de etilo (50 mL). La mezcla se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), y se redujo *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con 0-10% metanol en acetato de etilo, para producir el compuesto deseado como una espuma blanca (64 mg).

^{1}H NMR δ ($CDCl_3$): 1.29 (d, 3H), 2.38 (quintete, 2H), 2.49 (s, 3H), 2.72 (s, 1H), 3.75 - 3.77 (m, 2H), 4.20 - 4.41 (m, 4H), 4.51 - 4.59 (m, 1H), 6.95 (t, 1H), 6.99 (d, 1H), 7.35 (t, 1H), 7.37 - 7.38 (m, 1H), 8.05 - 8.08 (m, 1H), 8.40 (d, 1H)$_3$ 11.08 (s, 1H); *m/z* 470 $(M+H)^+$.

La preparación de 5-(azetidin-1-ilcarbonil)-2-cloropiridina se describió anteriormente.

La preparación de 3-hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(3-metil-1,2,4-tiadiazol-5-il)benzamida se describe a continuación.

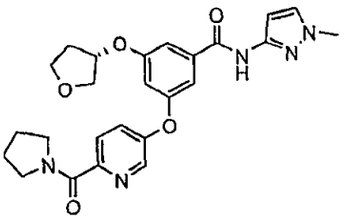
3-Hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(3-metil-1,2,4-tiadiazol-5-il)benzamida



Yodotrimetilsilano (5.51 mL, 38.7 mmol) se agregó a 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-(3-metil-1,2,4-tiadiazol-2-il)benzamida (2.5 g, 7.73 mmol) en acetonitrilo (25 mL) y la reacción se agitó a temperatura de la sala durante 48 horas. Metanol (15 mL) se agregó y la reacción se agitó durante 1 hora, luego se agregó una solución saturada de tiosulfato de sodio (10 mL) y se agitó durante 20 minutos. Los volátiles se retiraron *in vacuo* y el residuo acuoso se extrajo en acetato de etilo (2 x 150 mL). Los orgánicos se lavaron con agua, salmuera, se secaron ($MgSO_4$), y se redujeron *in vacuo* para producir un sólido amarillo. El sólido se trituró con DCM y luego con acetato de etilo para producir el compuesto deseado como un sólido blanco (1.44 g). ^{1}H NMR δ (d_6-DMSO): 1.23 (d, 3H), 2.49 (s, 3H), 3.46 - 3.59 (m, 2H), 4.48 - 4.52 (m, 1H), 4.89 (t, 1H), 6.60 (s, 1H), 7.08 (s, 1H), 7.24 (s, 1H), 9.91 (s, 1H), 13.28 (s, 1H); *m/z* 310 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*S*)-2-metoxi-(1-metiletil)oxi}-*N*-(3-metil-1,2,4-tiadiazol-2-il)benzamida se describió anteriormente.

Ejemplo 56: *N*-(1-metil-1*H*-pirazol-3-il)-3-{[6-(pirrolidin-1-ilcarbonil) piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida



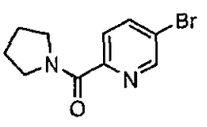
Yoduro de cobre (I) (95 mg, 0.5 mmol), 2,2,6,6-tetrametil-3,5-heptanodiona (0.42 mL, 2.0 mmol) y carbonato de cesio (489 mg, 1.5 mmol) se agregaron a una solución de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida (152 mg, 0.5 mmol) y 5-bromo-2-(pirrolidin-1-ilcarbonil)piridina (141 mg, 0.55 mmol) en NMP (5 mL), y la mezcla agitada se calentó a 160°C en un reactor microondas durante 12 horas. La mezcla se enfrió a temperatura y presión de la sala, la mezcla se repartió en porciones entre agua (75 mL) y acetato de etilo (50 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con acetato de etilo, para producir el material deseado (81 mg).

^{1}H NMR δ ($CDCl_3$): 1.8 - 1.95 (m, 4H), 2.0 - 2.2 (m, 2H), 3.6 (m, 2H), 3.75 (s, 3H), 3.85 (m, 2H), 3.95 (m, 2H), 4.9 (m, 1H), 6.65 (m, 1H), 6.75 (m, 1H), 7.1 (m, 1H), 7.2 (s, 1H), 7.25 (m, 1H), 7.3 (dd, 1H), 7.8 (d, 1H), 8.25 (d, 1H), 8.8 (s, 1H); *m/z* 478 $(M+H)^+$.

La preparación de 3-hidroxi-*N*-(1-metil-1*H*-pirazol-3-il)-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida se describió anteriormente.

La preparación de 5-bromo-2-(pirrolidin-1-ilcarbonil)piridina se describe a continuación.

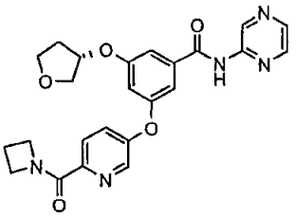
5-Bromo-2-(pirrolidin-1-ilcarbonil)piridina



Cloruro de oxalilo (0.83 mL; 9.3 mmol) y DMF (1 drop) se agregaron a una solución de ácido 5-bromoisonicotínico (1.57 g; 7.75 mmol) y 4M cloruro de hidrógeno en dioxano (1.93 mL; 7.75 mmol) en DCM (50 mL). La

mezcla se agitó a temperatura de la sala durante 18 horas, el DCM se retiró *in vacuo* y el residuo se destiló bajo una temperatura fija con tolueno (2 x 15 mL). El residuo se agregó a una solución de pirrolidina (0.78 mL; 9.3 mmol) y trietilamina (2.6 mL; 18.6 mmol) en DCM (40 mL), y la mezcla se agitó a temperatura de la sala durante 6 horas. El DCM se retiró *in vacuo*, el residuo se repartió en porciones entre agua (75 mL) y acetato de etilo (100 mL), la capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el material deseado (1.40 g). ^1H NMR δ ($CDCl_3$): 1.85 (m, 4H), 3.6 (m, 2H), 3.7 (s, 3H), 7.7 (d, 1H), 7.85 (s, 1H), 8.55 (s, 1H); *m/z* 257 $(M+H)^+$.

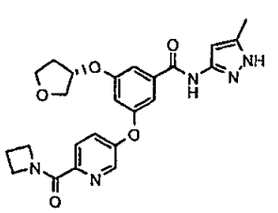
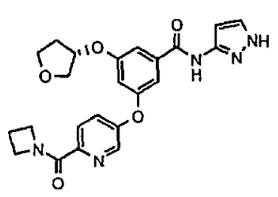
Ejemplo 57: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-pirazin-2-il-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.095 mL, 0.75 mmol) se agregó a una solución de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico (250 mg, 0.65 mmol) en DCM (6 mL) y se agitó a temperatura de la sala durante 30 - 40 minutos. Se agregaron 2-aminopirazina (125 mg, 1.31 mmol) y piridina (0.106 mL, 1.31 mmol), y la reacción se agitó a temperatura de la sala durante 2 horas. El disolvente se retiró *in vacuo*, se agregó agua (20 mL) y la mezcla se extrajo con acetato de etilo (3 x 20 mL). Los extractos orgánicos se combinaron y se lavaron con 2*N* ácido clorhídrico (20 mL), una solución saturada de bicarbonato de sodio (20 mL), agua (20 mL), salmuera (20 mL), se secaron ($MgSO_4$) y se evaporaron *in vacuo*. El producto crudo se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en DCM, para producir el compuesto deseado (71 mg).

^{1}H NMR δ ($CDCl_3$): 2.13 - 2.30 (m, 2H), 2.32 - 2.39 (m, 2H), 3.89 - 4.04 (m, 4H), 4.25 (t, 2H), 4.71 (t, 2H), 4.97 - 5.01 (m, 1H), 6.77 (t, 1H), 7.16 (t, 1H), 7.25 (s, 1H), 7.40 (dd, 1H), 8.14 (d, 1H), 8.28 (dd, 1H), 8.34 (d, 1H), 8.38 (s, 1H), 8.40 (d, 1H), 9.66 (d, 1H); *m/z* 462 $(M+H)^+$, 460 $(M-H)^-$.

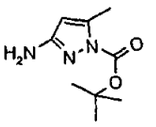
Los siguientes compuestos se prepararon en una forma análoga de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzoico y 1,1-dimetiletil 3-amino-5-metil-1*H*-pirazol-1-carboxilato o 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato. El material producido se disolvió en acetonitrilo (3mL) y se calentó a 150°C en un reactor microondas durante 10 minutos para producir el material deseado luego de la cromatografía.

Ejemplo	Estructura	m/z	NMR
57a		464 $(M+H)^+$ 462 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.12 - 2.27 (2H, m), 2.31 - 2.39, (2H, m), 2.33 (3H, s), 3.87 - 4.01 (4H, m), 4.24 (2H, t), 4.70 (2H, t), 4.95 - 4.98 (1H, m), 6.57 (1H, s), 6.73 (1H, t), 7.13 (1H, t), 7.24 (1H, t), 7.35 - 7.38 (1H, m), 8.10 (1H, d), 8.31 (1H, d), 8.79 (1H, s)
57b		450 $(M+H)^+$ 448 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.11 - 2.27 (2H, m), 2.30 - 2.38 (2H, m), 3.87 - 4.02 (4H, m), 4.22 (2H, t), 4.69 (2H, t), 4.95 - 4.97 (1H, m), 6.74 (1H, t), 6.77 (1H, s), 7.19 (1H, s), 7.30 (1H, s), 7.32 - 7.35 (1H, m), 7.51 (1H, d), 8.06 (1H, d), 8.30 (1H, d), 9.59 (1H, s)

Las preparaciones de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico y 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se describieron anteriormente.

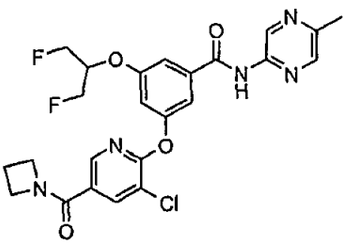
La preparación de 1,1-dimetiletil 3-amino-5-metil-1*H*-pirazol-1-carboxilato se describe a continuación.

1,1-Dimetiletil 3-amino-5-metil-1*H*-pirazol-1-carboxilato



5-Metil-1*H*-pirazol-3-amina (800 mg, 8.25 mmol) se disolvió en DMF (10 mL) a 0 °C y se trató con hidruro de sodio (336 mg, 8.25 mmol), seguido por agitación durante 30 minutos más. Luego se agregó lentamente di-*terc*-butil dicarbonato calentado (1.80 g, 8.25 mmol) mediante una jeringa durante 5 minutos, y la reacción se dejó calentar a temperatura de la sala y se agitó durante 1 hora más. La reacción se tomó en bicarbonato de sodio acuoso saturado (50 mL) y acetato de etilo (100 mL). La capa orgánica se separó, luego se secó ($MgSO_4$), se filtró y se evaporó. La purificación por cromatografía en columna, eluyendo con 50-100% acetato de etilo en isohexano, produjo el compuesto del título como un aceite incoloro (380 mg). ^{1}H NMR δ ($CDCl_3$): 1.62 (s, 9H), 2.43 (s, 3H), 3.87 (br. s, 2H), 5.60 (s, 1H).

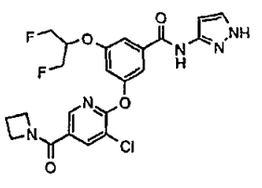
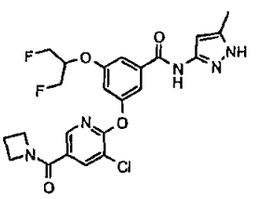
Ejemplo 58 : 3-{[5-(Azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida

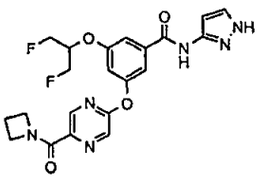
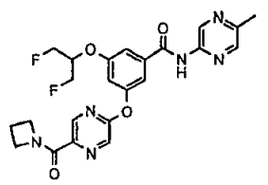


1-Cloro-*N*,*N*-2-trimetilpropenilamina (0.08 mL, 0.60 mmol) se agregó a una solución de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoico (215 mg, 0.5 mmol) en DCM (5 mL) y la reacción se agitó a temperatura de la sala durante 30 - 40 minutos. Se agregaron piridina (0.08 mL, 1.0 mmol) y 2-amino-5-metilpirazina (108 mg, 1.0 mmol), y la reacción se agitó durante 16 horas antes de concentrarse *in vacuo* y agregar agua (20 mL). La mezcla se extrajo con acetato de etilo (3 x 20 mL), se lavó con 1N ácido clorhídrico (20 mL), una

solución saturada de bicarbonato de sodio (20 mL), salmuera (20 mL), se secó ($MgSO_4$) y se concentró *in vacuo*. El producto crudo se cromatografió en sílice, eluyendo con una gradiente de 0-10% metanol en DCM, para producir el compuesto deseado como un sólido blanco (150 mg). ^{1}H NMR δ ($CDCl_3$): 2.40 (quintete, 2H), 2.56 (s, 3H), 4.22-4.31 (m, 2H), 4.32-4.40 (m, 2H), 4.62 - 4.82 (m, 5H), 7.06 (t, 1H), 7.38 (t, 1H), 7.47 (t, 1H), 8.15 (s, 1H), 8.17 (s, 1H), 8.25 (d, 1H), 8.46 (s, 1H), 9.55 (s, 1H); *m/z* 518 $(M+H)^+$, 516 $(M-H)^-$.

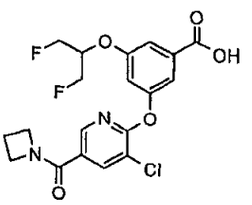
Los siguientes compuestos se prepararon en una forma análoga del ácido benzoico apropiado y 2-amino-5-metilpirazina, 1,1-dimetiletil 3-amino-5-metil-1*H*-pirazol-1-carboxilato o 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato. En los casos en donde se utilizaron 1,1-dimetiletil 3-amino-5-metil-1*H*-pirazol-1-carboxilato o 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato, se requirió un paso adicional para obtener el material deseado. Este paso adicional requería que el material se disolviera en acetonitrilo (3mL) y se calentara a 150°C en un reactor microondas durante 10 minutos; seguidamente el material deseado se aisló luego de la cromatografía.

Ejemplo	Estructura	m/z	NMR
58a		492 $(M+H)^+$ 490 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.39 (quin, 2H), 4.22 (t, 2H), 4.33 (t, 2H), 4.59 - 4.81 (m, 5H), 6.86 (s, 1H), 6.99 (s, 1H), 7.37 (s, 1H), 7.41 (s, 2H), 8.16 (d, 1H), 8.19 (d, 1H), 10.32 (s, 1H)
58b		506 $(M+H)^+$ 504 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.24 (s, 3H), 2.38 (quin, 2H), 4.23 (t, 2H), 4.34 (t, 2H), 4.59 - 4.79 (m, 5H), 6.59 (s, 1H), 7.00 (t, 1H), 7.34 (s, 1H), 7.37 (s, 1H), 8.16 (d, 1H), 8.19 (d, 1H), 9.95 (s, 1H)

58c		459 $(M+H)^+$ 457 $(M-H)^-$	^{1}H NMR8 (d_6-DMSO): 2.25-2.35 (m, 2H), 4.12-4.18 (m, 2H), 4.50 - 4.70 (m, 7H), 6.65 (s, 1H), 6.9 (s, 1H), 7.35 (s, 1H), 7.37 (s, 1H), 7.45 (s, 1H), 8.25 (s, 1H), 8.70 (s, 1H), 10.60 (s, 1H)
58d		485 $(M+H)^+$ 483 $(M-H)^-$	^{1}H NMR δ ($CDCl_3$): 2.34 - 2.42 (m, 2H), 2.58 (s, 3H), 4.26 (t, 2H), 4.69 (t, 2H), 4.63 -4.81 (m, 5H), 7.05 (t, 1H), 7.37 (t, 1H), 7.45 -7.46 (m, 1H), 8.14 (d, 1H), 8.34 (s, 1H), 8.37 (d, 1H), 8.86 (d, 1H), 9.53 (d, 1H)

Las preparaciones de 1,1-dimetiletil 3-amino-5-metil-1*H*-pirazol-1-carboxilato o 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se describieron anteriormente. La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoico se describe a continuación.

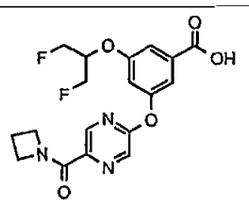
Ácido 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoico



Una mezcla de metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoato (3.6 g, 8.2 mmol) en THF (50 mL) y agua (50 mL) se trató con 1M solución de hidróxido de sodio (8.2 mL, 8.2 mmol) y se dejó agitando a temperatura de la sala durante 210 minutos. El THF se retiró *in vacuo*, el residuo se filtró y se extrajo con acetato de etilo (30 mL). La capa acuosa se acidificó con 2N ácido clorhídrico, se extrajo con acetato de etilo (3 x 50 mL), y los extractos orgánicos combinados se lavaron con agua (10 mL), salmuera (10 mL) y se concentraron *in vacuo* para producir el material deseado como una espuma

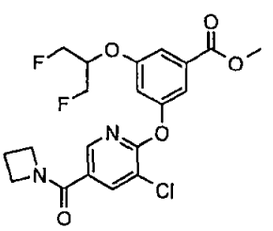
amarillo pálido (2.84 g). ^{1}H NMR δ ($CDCl_3$): 2.36 - 2.44 (m, 2H), 4.26 (t, 2H), 4.37 (t, 2H), 4.62 - 4.79 (m, 5H), 7.08 (t, 1H), 7.56 - 7.57 (m, 1H), 7.58 - 7.59 (m, 1H), 8.17 (d, 1H), 8.27 (d, 1H); *m/z* 426 $(M+H)^+$, 424 $(M-H)^-$.

Ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil) etil]oxi}benzoico se preparó en una forma análoga de metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil] oxi}benzoato.

Estructura	m/z	NMR
	394 $(M+H)^+$ 392 $(M-H)^-$	^{1}H NMR δ (d_6-DMSO): 2.26 - 2.34 (m, 2H), 4.08 - 4.15 (m, 2H), 4.56 (t, 2H), 4.60 - 5.10 (m, 5H), 7.29 (t, 1H), 7.38 - 7.39 (m, 1H), 7.46 -7.47 (m, 1H), 8.56 (d, 1H), 8.65 - 8.67 (m, 1H)

La preparación de metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoato se describe a continuación.

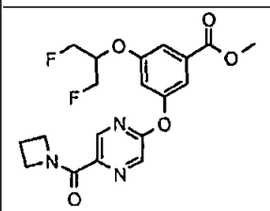
Metil 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoato



Una solución de metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxibenzoato (1.78 g, 7.24 mmol), carbonato de potasio (2.0 g, 14.5 mmol) y 5-(azetidin-1-ilcarbonil)-2,3-dicloropiridina (2.08 g, 8.7 mmol) en acetonitrilo (15mL) se calentó en un reactor microondas a 130°C durante 1 hora. La solución se diluyó con acetato de etilo (150 mL), se lavó con agua (3 x 50 mL), salmuera (20 mL), se secó ($MgSO_4$), y el disolvente se retiró *in vacuo* para producir el material deseado como un aceite anaranjado (3.6

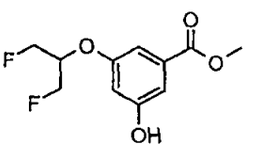
g). ^{1}H NMR δ ($CDCl_3$): 2.35 - 2.44 (m, 2H), 3.91 (s, 3H), 4.24 - 4.27 (m, 2H), 4.34 - 4.37 (m, 2H), 4.62 - 4.81 (m, 5H), 7.04 (t, 1H), 7.51 (t, 1H), 7.55 (m, 1H), 8.15 (d, 1H), 8.25 (d, 1H); *m/z* 441 $(M+H)^+$.

Metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzoato se preparó en una forma análoga de metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxibenzoato.

Estructura	m/z	NMR
	408 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 2.34 - 2.43 (m, 2H), 3.91 (s, 3H), 4.26 (t, 2H), 4.59 - 4.79 (m, 5H), 4.65 - 4.71 (m, 2H), 7.03 (t, 1H), 7.49 - 7.50 (m, 1H), 7.54 -7.55 (m, 1H), 8.33 (d, 1H), 8.84 - 8.86 (m, 1H)

La preparación de metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxibenzoato se describe a continuación.

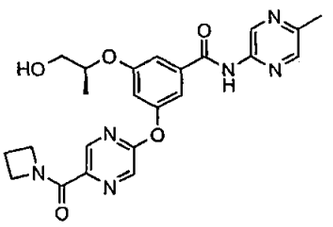
Metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-hidroxibenzoato



10% Paladio sobre carbón vegetal (Pd/C; 50 mg) se agregó a una mezcla de metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi]benzoato (1.2 g, 3.62 mmol) y formiato de amonio (500 mg, 8.0 mmol) en etanol (7 mL) y luego se calentó a 140°C durante 20 minutos en un reactor microondas. La reacción se repitió en la misma escala y las dos mezclas de reacción se combinaron, se filtraron, y el filtrado se concentró *in vacuo* para producir el material deseado como un aceite amarillo pálido (2.1 g). ^{1}H NMR δ ($CDCl_3$): 3.82 (s, 3H), 4.58 - 4.77 (m, 5H), 6.72 (t, 1H), 7.17 - 7.22 (m, 2H); *m/z* 245 $(M-H)^-$.

La preparación de metil 3-{[2-fluoro-1-(fluorometil)etil]oxi}-5-[(fenilmetil)oxi]benzoato se describió anteriormente.

Ejemplo 59: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida

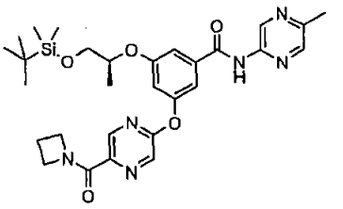


1M Ácido clorhídrico (5 mL) se agregó a una solución de 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida (90 mg, 0.16 mmol) en metanol (5 mL) y la mezcla se agitó a temperatura de la sala durante 1 hora. El metanol se retiró *in vacuo*, el residuo se ajustó a pH6 y luego se extrajo en acetato de etilo (3 x 50 mL). Los orgánicos combinados se lavaron con salmuera (50 mL), se secaron ($MgSO_4$), y se redujeron *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-5% metanol en acetato de etilo, para producir el compuesto deseado como una espuma blanca (28 mg).

^{1}H NMR δ ($CDCl_3$): 1.33 (d, 3H), 2.11 (s, 1H), 2.38 (quintete, 2H), 2.55 (s, 3H), 3.74 - 3.82 (m, 2H), 4.26 (t, 2H), 4.55 - 4.62 (m, 1H), 4.69 (t, 2H), 6.97 (t, 1H), 7.30 (t, 1H), 7.40 (t, 1H), 8.13 (s, 1H), 8.35 (d, 1H), 8.41 (s, 1H), 8.85 (d, 1H), 9.53 (d, 1H); *m/z* 465 $(M+H)^+$.

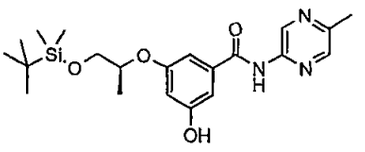
La preparación de 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il) benzamida se describe a continuación.

3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il) benzamida



Una mezcla de 3-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-(5-metilpirazin-2-il)benzamida (0.12 g, 0.29 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (57 mg, 0.29 mmol) y carbonato de potasio (80 mg, 0.57 mmol) en acetonitrilo (5 mL) se agitó en un reactor microondas a 140°C durante 1 hora. La mezcla se redujo *in vacuo* y se agregó acetato de etilo (50 mL). La mezcla se lavó con agua (50 mL), salmuera (50 mL), se secó ($MgSO_4$), se filtró y se redujo *in vacuo* para producir un aceite marrón, el cual se cromatografió en sílice, eluyendo con 50 a 100% acetato de etilo en isohexano, para producir el compuesto deseado como un aceite incoloro (90 mg). ^{1}H NMR δ ($CDCl_3$): - 0.03 (s, 3H), 0.00 (s, 3H), 0.81 (s, 9H), 1.26 (d, 3H), 2.32 (quintete, 2H), 2.49 (s, 3H), 3.61 - 3.76 (m, 2H), 4.20 (t, 2H), 4.46 (sextete, 1H), 4.62 (t, 2H), 6.91 (t, 1H), 7.21 (t, 1H), 7.32 (t, 1H), 8.07 (s, 1H), 8.28 (d, 1H), 8.30 (s, 1H), 8.79 (d, 1H), 9.48 (d, 1H). *m/z* 579 $(M+H)^+$.

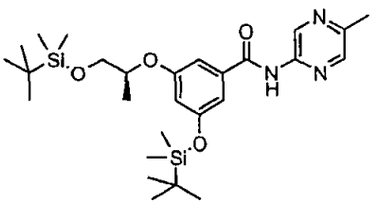
3-[((1*S*)-2-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-5-hidroxi-*N*-(5-metilpirazin-2-il)benzamida



Monohidrato de hidróxido de litio (0.38 g, 9.12 mol) en agua (20 mL) se agregó a una solución de 3-{[(1,1-dimetiletil)(dimetil)silil]oxi}-5-[((1*S*)-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il) benzamida (1.94 g, 3.65 mol) en THF (40 mL) y se agitó a temperatura de la sala durante 20 horas. El THF se retiró *in vacuo* y la capa acuosa se ajustó a pH7. Acetato de etilo (50 mL) y agua (50 mL) se agregaron, en seguida la capa acuosa se re-extrajo en acetato de etilo (50 mL) y los

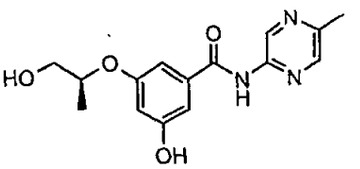
orgánicos combinados se lavaron con agua (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo*. El material crudo se cromatografió en sílice, eluyendo con 20-50% acetato de etilo en isohexano, para producir el material deseado como un sólido blanco (0.8 g). ^{1}H NMR δ ($CDCl_3$): 0.04 (s, 3H), 0.08 (s, 3H), 0.87 (s, 9H), 1.30 (d, 3H), 2.56 (s, 3H), 3.65 - 3.81 (m, 2H), 4.46 - 4.51 (m, 1H), 5.63 (s, 1H), 6.63 (t, 1H), 6.98 (t, 1H), 7.04 (t, 1H), 8.15 (s, 1H), 8.41 (s, 1H), 9.57 (s, 1H); *m/z* 418 $(M+H)^+$.

3-{[(1,1-Dimetiletil)(dimetil)silil]oxi}-5-[((1*S*))-2-{[(1,1-dimetiletil)(dimetil)silil]oxi}-1-metiletil)oxi]-*N*-(5-metilpirazin-2-il)benzamida



terc-Butildimetilsilil cloruro (2.61 g, 17.31 mmol) se agregó a una solución de 3-hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida (1.5 g, 4.95 mmol) e imidazol (2.36 g, 34.62 mmol) en DMF (15 mL), y la reacción se agitó a temperatura de la sala durante 24 horas. Se agregó agua y el producto se extrajo en éter (2 x 100 mL). Los orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo* para producir un aceite amarillo, el cual se cromatografió en sílice, eluyendo con 0-40% acetato de etilo en isohexano, para producir el material deseado como un aceite incoloro (1.94 g). ^{1}H NMR δ ($CDCl_3$): -0.03 (s, 3H), 0.01 (s, 3H), 0.16 (s, 6H), 0.81 (s, 9H), 0.92 (s, 9H), 1.23 (d, 3H), 2.48 (s, 3H), 3.58 - 3.74 (m, 2H), 4.37 - 4.42 (m, 1H), 6.54 (t, 1H), 6.86 (t, 1H), 6.99 (t, 1H), 8.06 (s, 1H), 8.21 (s, 1H), 9.48 (d, 1H).

3-Hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida



Yoduro de trimetilsililo (6.06 mL, 42.75 mmol) se agregó a una solución de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il) benzamida (2.71 g, 8.55 mmol) en acetonitrilo seco (150 mL) y se agitó durante 24 horas. Se agregó metanol (30 mL) para extinguir la reacción y se agitó durante 10 minutos. Se agregó 10% o/v de pentahidrato de tiosulfato de sodio acuoso (20 mL) a la mezcla y se retiraron los disolventes orgánicos *in vacuo*. El residuo se llevó a pH5 con 1M ácido clorhídrico y se agregó acetato de etilo (80 mL). Un sólido amarillo (1.4 g) se separó por filtración. El filtrado acuoso se re-extrajo en acetato de etilo (2x80 mL) y las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y los disolventes se retiraron *in vacuo*. Este residuo se combinó con el sólido amarillo obtenido anteriormente y se purificó por cromatografía en columna, eluyendo con 5% a 10% metanol en DCM, para producir el compuesto del título (1.70 g) ^{1}H. NMR δ (d_6-DMSO): 1.21 (d, 3H), 2.50 (s, 3H), 3.40-3.60 (m, 2H), 4.45 (sex, 1H), 4.80 (t, 1H), 6.50 (s, 1H), 6.97 (s, 1H), 7.08 (s, 1H), 8.32 (s, 1H), 9.21 (s, 2H), 9.63 (s, 1H), 10.80 (brs, 1H). *m/z* 304 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida se describió anteriormente.

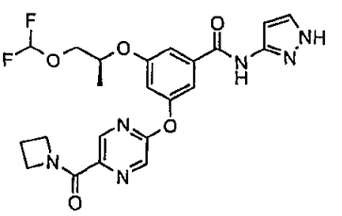
Ejemplo 59, 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida se preparó también en la siguiente manera.

Una mezcla de 3-hidroxi-5-{[(1*S*)-2-hidroxi-1-metiletil]oxi}-*N*-(5-metilpirazin-2-il)benzamida (3.03 g, 10.0 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (2.17 g, 11.0 mmol) y carbonato de potasio (4.14 g, 30.0

mmol) en acetonitrilo (30.3 mL) se calentó a 60°C de un día para otro. El disolvente se retiró por evaporación y el residuo se repartió en porciones entre acetato de etilo (15 vol) y agua (10 volúmenes). La fase acuosa se extrajo posteriormente en acetato de etilo y los orgánicos combinados se lavaron con agua, salmuera, se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo*. El residuo se cromatografió en sílice, eluyendo con 0.5-6% metanol en acetato de etilo, para producir el material deseado como una espuma (3.1 g). Una muestra de este material (100 mg) se disolvió en el volumen mínimo de acetonitrilo, luego se agregó isohexano (5 mL). La mezcla se agitó durante 3 días, se decantó el líquido y el residuo se trituró con éter dietílico. El material cristalino se recogió por filtración. ^{1}H NMR δ (d_6-DMSO): 1.25 (d, 3H), 2.30 (quintete, 2H), 2.48 (s, 3H), 3.49 - 3.61 (m, 2H), 4.09 (t, 2H), 4.55 - 4.63 (m, 3H), 4.92 (t, 1H), 7.12 (t, 1H), 7.47 (t, 1H), 7.57 (t, 1H), 8.37 (d, 1H), 8.58 (d, 1H), 8.69 (d, 1H), 9.26 (d, 1H), 11.06 (s, 1H); *m/z* 465 $(M+H)^+$. Mpt (iniciación de la fusión) 100.6°C.

El compuesto del título se cristalizó igualmente agitando una suspensión del compuesto en acetato de etilo (punto de fusión 125.0°C), tolueno, nitrometano o metanol.

Ejemplo 60: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-*N*-1*H*-pirazol-3-ilbenzamida



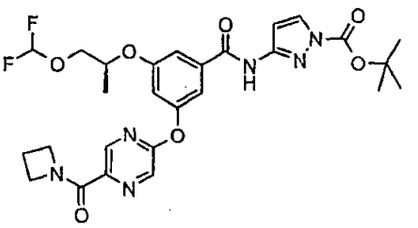
Ácido trifluoroacético (2 mL) se agregó a una solución de 1,1-dimetiletil 3-({[3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil) oxi]-1-metiletil}oxi)fenil]carbonil}amino)-1*H*-pirazol-1-carboxilato (115 mg, 0.17 mmol) en DCM (16 mL) y se agitó a temperatura de la sala durante 2 horas. El disolvente se retiró *in vacuo*, se agregó DCM (20 mL) y

la mezcla se lavó con agua (20 mL), una solución saturada de bicarbonato de sodio (20 mL), salmuera (20 mL), se secó ($MgSO_4$), se filtró y se redujo *in vacuo* para producir el compuesto deseado como una espuma blanca (93 mg).

^{1}H NMR δ ($CDCl_3$): 1.36 (d, 3H), 2.37 (quintete, 2H), 3.93 - 4.02 (m, 2H), 4.24 (t, 2H), 4.59 - 4.69 (m, 3H), 6.24 (t, 1H), 6.82 (s, 1H), 6.89 (t, 1H), 7.29 - 7.31 (m, 1H), 7.36 - 7.38 (m, 1H), 7.40 (d, 1H), 8.35 (d, 1H), 8.79 (d, 1H), 10.23 (s, 1H), 10.48 (s, 1H); *m/z* 489 $(M+H)^+$.

La preparación de 1,1-dimetiletil 3-({[3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)fenil]carbonil} amino)-1*H*- pirazol-1-carboxilato se describe a continuación.

1,1-Dimetiletil 3-({[3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)fenil]carbonil}amino)-1*H*-pirazol-1-carboxilato



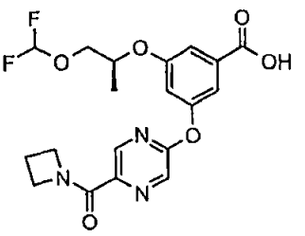
1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.12 mL, 0.92 mmol) se agregó a una solución de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1S)-2-[(difluorometil)oxi]-1-metiletil}oxi)benzoico (0.26 g, 0.61 mmol) en DCM (8 mL) y se agitó durante 1 hora. Se agregaron 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato (169 mg, 0.92 mmol), luego piridina (0.1 mL, 1.23 mmol) y se agitó durante 20 horas más. La mezcla de reacción se redujo *in vacuo* y se agregaron acetato de etilo (50 mL) y agua (50 mL). La capa acuosa se re-extrajo en acetato de etilo (50 mL) y los orgánicos combinados se lavaron con agua (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo*. El aceite crudo se cromatografió en sílice, eluyendo con 25-50% acetato de etilo en isohexano,

para producir el compuesto deseado como un aceite incoloro (100 mg). ^{1}H NMR δ ($CDCl_3$): 1.38 (d, 3H), 1.62 (s, 9H), 2.38 (quintete, 2H), 3.93 - 4.04 (m, 2H), 4.26 (t, 2H), 4.61 - 4.65 (m, 1H), 4.69 (t, 2H), 6.26 (t, 1H), 6.95 (t, 1H), 7.08 (d, 1H), 7.25 - 7.26 (m, 1H), 7.33 (t, 1H), 8.01 (d, 1H), 8.34 (d, 1H), 8.84 (s, 1H), 8.85 (d, 1H); *m/z* 587 $(M-H)^-$.

La preparación de 1,1-dimetiletil 3-amino-1*H*-pirazol-1-carboxilato se describió anteriormente.

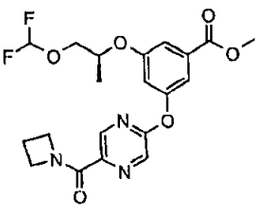
La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2- [(difluorometil)oxi]-1-metiletil}oxi)benzoico se describe a continuación.

Ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil) oxi]-1-metiletil}oxi)benzoico



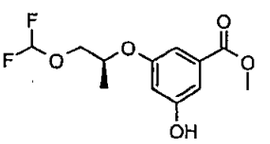
Monohidrato de hidróxido de litio (48 mg, 1.13 mmol) en agua (5 mL) se agregó a una solución de metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)benzoato (0.33 g, 0.75 mmol) en THF (10 mL) y se agitó a temperatura de la sala durante 20 horas. El THF se retiró *in vacuo* y la capa acuosa se lavó con acetato de etilo (50 mL) para retirar posibles impurezas. La capa acuosa se acidificó y se extrajo en acetato de etilo (2 x 50 mL), se lavó con salmuera, se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo* para producir el compuesto deseado como una espuma blanca (0.26 g). *m/z* 424 $(M+H)^+$.

Metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxil-5-({(1*S*)-2-[(difluorometil) oxil-1-metiletil}oxi)benzoato



Una mezcla de metil 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxibenzoato (0.28 g, 1.01 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (201 mg, 1.01 mmol) y carbonato de potasio (280 mg, 2.03 mmol) en acetonitrilo (5 mL) se agitó en un reactor microondas a 140°C durante 5 horas. La mezcla de reacción se redujo *in vacuo*, se agregó acetato de etilo (50 mL) y los orgánicos se lavaron con agua (50 mL), salmuera (50 mL), se secaron ($MgSO_4$), se filtraron y se redujeron *in vacuo*. El aceite crudo se cromatografió en sílice, eluyendo con 20 a 70% acetato de etilo en isohexano, para producir el compuesto deseado como un aceite incoloro (330 mg). ^{1}H NMR δ ($CDCl_3$): 1.38 (d, 3H), 2.37 (quintete, 2H), 3.90 (s, 3H), 3.93 - 4.04 (m, 2H), 4.26 (d, 2H), 4.61 - 4.70 (m, 3H), 6.25 (t, 1H), 6.95 (t, 1H), 7.43 - 7.44 (m, 1H), 7.49 - 7.50 (m, 1H), 8.32 (d, 1H), 8.85 (d, 1H); *m/z* 438 $(M+H)^+$.

Metil 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-hidroxibenzoato

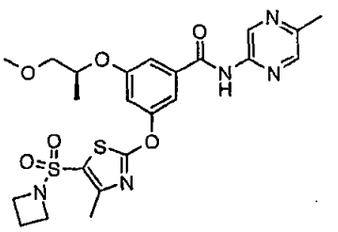


Metil 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-[(fenilmetil)oxi] benzoato (0.48 g, 1.08 mmol) se disolvió en etanol (10 mL) y THF (10 mL) y el matraz se vació y se purgó con argón (3 veces). Se agregó 10% paladio sobre carbón (140 mg) y el matraz se volvió a vaciar y, finalmente, se purgó con gas hidrógeno. La mezcla de reacción se agitó a temperatura de la sala durante 20 horas hasta que se completó. La mezcla de reacción se vació y purgó con argón (3 veces), luego se retiró el catalizador por filtración a través de Celite®. El filtrado se concentró *in vacuo* para producir el compuesto deseado como un aceite incoloro (1.05 g). ^{1}H NMR δ ($CDCl_3$): 1.35 (d, 3H), 3.90 (s, 3H), 3.90 - 4.02 (m, 2H), 4.57 - 4.64 (m, 1H), 5.20 (s,

1H), 6.26 (t, 1H), 6.63 (t, 1H), 7.14 - 7.15 (m, 1H), 7.17 - 7.18 (m, 1H); *m/z* 275 $(M-H)^-$.

Las preparaciones de metil 3-({(1*S*)-2-[(difluorometil)oxi]-1-metiletil}oxi)-5-[(fenilmetil)oxi]benzoato y 2-(azetidin-1-ilcarbonil)-5-cloropirazina se describieron anteriormente.

Ejemplo 61: 3-{[5-(Azetidin-1-ilsulfonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida

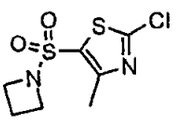


Carbonato de cesio (293 mg, 0.9 mmol) se agregó a una solución de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il) benzamida (95 mg, 0.3 mmol) y 5-(azetidin-1-ilsulfonil)-2-cloro-4-metil-1,3-tiazol (90 mg, 0.36 mmol) en acetonitrilo (5 mL) y la mezcla agitada se calentó en un reactor microondas a 120°C durante 1 hora. La mezcla se enfrió a temperatura y presión de la sala, el acetonitrilo se retiró *in vacuo*, y el residuo se repartió en porciones entre agua (15 mL) y acetato de etilo (30 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó *in vacuo* a un residuo, el cual se cromatografió en sílice, eluyendo con 60% acetato de etilo en isohexano, para producir el material deseado como un sólido incoloro (79 mg). ^1H NMR δ ($CDCl_3$): 1.3 (d, 3H), 2.15 (m, 2H), 2.5 (s, 3H), 2.5 (s, 3H), 3.35 (s, 3H), 3.45 - 3.55 (m, 2H), 3.85 (t, 4H), 4.55 (m, 1H), 7.0 (d, 1H), 7.35 (d, 2H), 8.05 (s, 1H), 8.3 (s, 1H), 9.45 (s, 1H); *m/z* 534 $(M+H)^+$.

La preparación de 3-hidroxi-5-{[(1*S*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida se describió anteriormente.

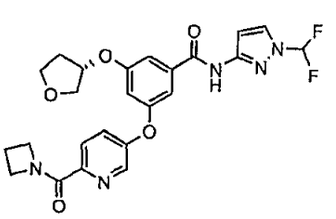
La preparación de 5-(azetidin-1-ilsulfonil)-2-cloro-4-metil-1,3-tiazol se describe a continuación.

5-(Azetidin-1-ilsulfonil)-2-cloro-4-metil-1,3-tiazol



Una solución de 2-cloro-4-metiltiazol-5-sulfonilcloruro (462 mg; 2.0 mmol) en DCM (5 mL) se agregó a una solución helada de clorhidrato de azetidina (196 mg; 2.1 mmol) y trietilamina (1.0 mL; 7.2 mmol) en DCM (15 mL), y la mezcla se agitó a 0°C durante 30 minutos. El DCM se retiró *in vacuo* para producir un residuo, el cual se repartió en porciones entre agua (50 mL) y acetato de etilo (75 mL). La capa orgánica se lavó con salmuera, se secó ($MgSO_4$) y se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con 10% acetato de etilo en isohexano, para producir el material deseado como un sólido, el cual se cristalizó de acetato de etilo e isohexano (100 mg). ^{1}H NMR δ ($CDCl_3$): 2.2 (dt, 2H), 2.65 (s, 3H), 3.9 (t, 4H); *m/z* 253 $(M+H)^+$.

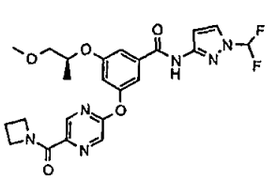
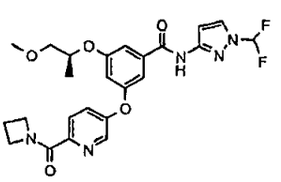
Ejemplo 62: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-[1-(difluorometil)-1*H*-pirazol-3-il]-5-[(3*S*)-tetrahidrofuran-3-iloxi] benzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.088 mL, 0.66 mmol) se agregó a una solución de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico (171 mg, 0.44 mmol) en DCM (10 mL) y la reacción se agitó a temperatura de la sala durante 30 minutos. Trascurrido este tiempo se agregaron consecutivamente clorhidrato de 1-(difluorometil)pirazol-3-amina (75 mg, 0.44 mmol) y DIPEA (0.154 mL, 0.89 mmol). La solución resultante se agitó a temperatura de la sala durante 16 horas, tiempo luego del cual el disolvente se retiró *in vacuo* y se

agregaron acetato de etilo (20 mL) y agua (20 mL). La fase acuosa se extrajo con acetato de etilo (2 x20 mL), se lavó con una solución saturada de bicarbonato de sodio (20 mL) y salmuera (20 mL). Los extractos orgánicos combinados se secaron ($MgSO_4$), se filtraron y se evaporaron. El residuo se purificó por cromatografía rápida en columna en sílice, eluyendo con 50-100% acetato de etilo en isohexano, para proporcionar el producto deseado como un sólido blanco (132 mg). ^{1}H NMR δ ($CDCl_3$): 2.40 - 2.12 (m, 4H), 4.03 - 3.89 (m, 4H), 4.25 (t, 2H), 4.71 (t, 2H), 5.01 - 4.96 (m, 1H), 6.76 (t, 1H), 7.03 (t, 1H), 7.08 (d, 1H), 7.11 (s, 1H), 7.22 (s, 1H), 7.38 (dd, 1H), 7.75 (d, 1H), 8.13 (d, 1H), 8.33 (d, 1H), 8.50 (s, 1H); ^{19}F NMR δ ($CDCl_3$): -93.84; *m/z* 500 $(M+H)^+$.

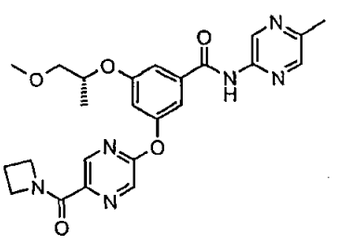
Los siguientes compuestos se elaboraron en una forma análoga.

Ejemplo	Estructura	m/z	NMR
62a		503 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.34 (d, 4H), 2.37 (quin, 2H), 3.40 (s, 3H), 3.51 (dd, 2H), 3.59 (dd, 2H), 4.25 (t, 2H), 4.60 (m, 1H), 4.68 (t, 2H), 6.96 (t, 1H), 7.02 (s, 1H), 7.02 (t, 1H), 7.08 (d, 1H), 7.26 (s, 1H), 7.37 (t, 1H), 7.73 (d, 1H), 8.33 (d, 1H), 8.54 (s, 1H), 8.85 (d, 1H)
62b		502 $(M+H)^+$	^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.24 - 2.32 (m, 2H), 3.46 - 3.55 (m, 2H), 4.08 (t, 2H), 4.59 (t, 2H), 4.77 (m, 1H), 6.89 (d, 1H), 6.97 (t, 1H), 7.30 (s, 1H)$_3$ 7.50 (s, 1H), 7.58 (dd, 1H), 7.71 (t, 1H), 8.00 (d, 1H), 8.15 (d, 1H), 8.42 (d, 1H), 11.22 (s, 1H)

Las preparaciones de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3*S*)-tetrahidrofuran-3-iloxi]benzoico, ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzoico y ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil] oxi}benzoico se describieron anteriormente.

La preparación de 1-(difluorometil)pirazol-3-amina se describe en la literatura [WO2005090332, PCT Int. Appl. (2005)].

Ejemplo 63: 3-{[5-(Azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida

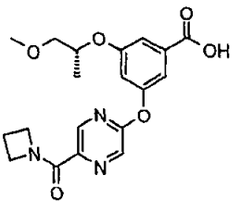


1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (0.042 mL, 0.31 mmol) se agregó a una solución de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}benzoico (0.102 g, 0.0.31 mmol) en DCM (3 mL) bajo argón y se agitó a temperatura de la sala durante 40 minutos. Se agregaron 2-amino-5-metilpirazina (57 mg, 0.52 mmol) y piridina (0.043 mL, 0.52 mmol), y la reacción se agitó durante 3 horas más. El disolvente se retiró *in vacuo* y el residuo se tomó en acetato de etilo (30 mL), se lavó con agua (2 x 10 mL), una solución acuosa saturada de bicarbonato de sodio (10 mL), salmuera (10 mL), se secó ($MgSO_4$), se filtró, y se evaporó *in vacuo*. El material crudo se cromatografió en sílice, eluyendo con una gradiente de 60-100% acetato de etilo en isohexano, para producir el compuesto deseado como una espuma blanca (86 mg).

^{1}H NMR δ ($CDCl_3$): 1.35 (d, 3H), 2.32 - 2.44 (m, 2H), 2.56 (s, 3H), 3.41 (s, 3H), 3.47 - 3.64 (m, 2H), 4.26 (t, 2H), 4.62 (q, 1H), 4.69 (t, 2H), 6.98 (s, 1H), 7.29 (s, 1H), 7.41 (s, 1H), 8.13 (s, 1H), 8.35 (s, 2H), 8.86 (s, 1H), 9.54 (s, 1H); *m/z* 479 $(M+H)^+$.

La preparación de ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}benzoico se describe a continuación.

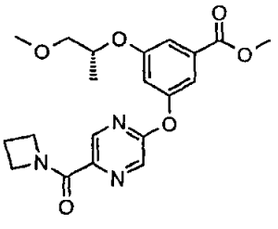
Ácido 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[1*R*)-1-metil-2-(metiloxi) etil]oxi]benzoico



Metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}benzoato (1.06 g, 2.6 mmol) se disolvió en THF (24 mL) y metanol (8 mL), luego se agregó una solución 1N de hidróxido de litio (3.12 mL), seguida por la adición gota a gota de agua (10 mL). La solución resultante se agitó durante 3 horas a temperatura de la sala, se agregó una porción más de la solución 1N de hidróxido de litio (1.3 mL), la reacción se agitó 2 horas más, luego se agregó más solución 1N de hidróxido de litio (0.6 mL) y se continuó la agitación durante 1 hora más. Los orgánicos se retiraron por evaporación bajo presión reducida, la solución acuosa se lavó con éter dietílico (10 mL), luego se acidificó con 2N ácido clorhídrico y se extrajo con acetato de etilo (3 x 20 mL). Los orgánicos combinados se lavaron con agua (10 mL), salmuera (10 mL) y se evaporaron a sequedad bajo presión reducida para producir el compuesto deseado como un sólido blanco (887 mg).

^{1}H NMR δ ($CDCl_3$): 1.34 (d, 3H), 2.38 (quintete, 2H), 3.41 (s, 3H), 3.47 - 3.64 (m, 2H), 4.27 (t, 2H), 4.55 - 4.65 (m, 1H), 4.69 (t, 2H), 6.99 (s, 1H), 7.45 (s, 1H), 7.55 (s, 1H), 8.33 (s, 1H), 8.84 (s, 1H); *m/z* 388 $(M+H)^+$.

Metil 3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}benzoato

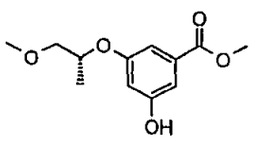


Una mezcla de metil 3-hidroxi-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi} benzoato (727 mg, 3 mmol), 2-(azetidin-1-ilcarbonil)-5-cloropirazina (712 mg, 3.6 mmol) y carbonato de potasio (828 mg, 6 mmol) en DMA (10 mL)

se agitó a 120°C durante 2 horas. La solución se diluyó con acetato de etilo (150 mL), se lavó con agua (3 x 50 mL), salmuera (20 mL), se secó ($MgSO_4$), se filtró, y el disolvente se retiró *in vacuo*. El residuo se purificó por cromatografía en sílice, eluyendo con 50% acetato de etilo en isohexano, para producir el material deseado como un aceite incoloro (1.07 g). ^{1}H NMR δ ($CDCl_3$): 1.27 (d, 3H), 2.4 (quintete, 2H), 3.4 (s, 3H), 3.5 - 3.6 (m, 2H), 3.9 (s, 3H), 4.25 (t, 2H), 4.53 (q, 1H), 4.7 (t, 2H), 6.95 (s, 1H), 7.4 (s, 1H), 7.5 (s, 1H), 8.3 (s, 1H), 8.85 (s, 1H); *m/z* 402 $(M+H)^+$.

La preparación de 2-(azetidin-1-ilcarbonil)-5-cloropirazina se describió anteriormente.

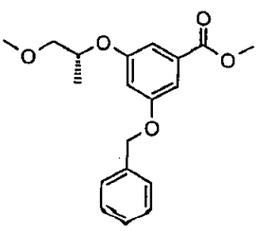
Metil 3-hidroxi-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}benzoato



Una solución de metil 3-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}-5- [(fenilmetil) oxi]benzoato en THF (5 mL) y etanol (5 mL), que contenía 10% paladio sobre carbón, se agitó bajo una atmósfera de hidrógeno durante 16 horas. El paladio sobre carbón se retiró por filtración y el filtrado se evaporó bajo presión reducida para producir el material deseado como una goma clara (723 mg).

^{1}H NMR δ ($CDCl_3$): 1.31 (d, 3H), 3.42 (s, 3H), 3.48 - 3.64 (m, 2H), 3.88 (s, 3H), 4.54 - 4.63 (m, 1H), 5.75 (s, 1H), 6.64 (s, 1H), 7.11 (s, 1H), 7.17 (s, 1H); *m/z* 241 $(M+H)^+$.

Metil 3-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}-5-[(fenilmetil)oxi]benzoato

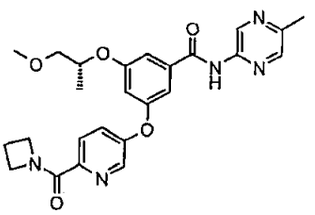


DIAD (4.6 g, 0.029mol) se agregó gota a gota a una solución de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (6 g, 0.023 mol), (*S*)-(+)-1-metoxi-2-propanol (2.59 g, 0.029 mol) y trifenilfosfina (7.53 g, 0.029 mol) en THF (100 mL), bajo argón, a 0°C. La reacción se agitó a 0°C durante 1 hora y a temperatura de la sala durante 20 horas. Los volátiles se retiraron *in vacuo* y se agregó isohexano / acetato de etilo 2:1, seguido por agitación durante 1 hora. Un sólido blanco se retiró por filtración, y el filtrado se evaporó a un residuo, el cual se cromatografió en sílice, eluyendo con una gradiente de 0-20% acetato de etilo en isohexano, para producir el compuesto deseado (5.11 g).

^{1}H NMR δ ($CDCl_3$): 1.31 (d, 3H), 3.40 (s, 3H), 3.45-3.60 (m, 2H), 3.88 (s, 3H), 4.57 (sex, 1H), 5.07 (s, 2H), 6.76 (m, 1H), 7.25 (m, 2H), 7.40 (m, 5H). *m/z* 331 $(M+H)^+$.

La preparación de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato se describió anteriormente.

Ejemplo 64: 3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}-*N*-(5-metilpirazin-2-il)benzamida

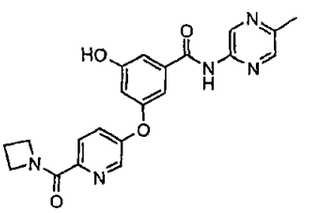


Una mezcla de 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-hidroxi-*N*-(5-metilpirazin-2-il)benzamida (101 mg, 0.25 mmol), S-(+)-metoxi-2-propanol (0.049 mL, 0.50 mmol) y trifenilfosfina (131 mg, 0.50 mmol) en THF seco (10 mL) se trató gota a gota con DIAD (0.099 mL, 0.50 mmol) a 0°C bajo una atmósfera de argón. La mezcla se dejó calentar a temperatura de la sala y se agitó de un día para otro. El THF se retiró por evaporación bajo presión reducida y el residuo se purificó dos veces por cromatografía en sílice, eluyendo con 0-7% metanol en DCM. Las fracciones deseadas se

combinaron y se purificaron mediante elución a través de una columna SCX, eluida con 5% metanol en DCM, luego 50% 7N amoníaco (en metanol) en DCM. Las fracciones deseadas se purificaron mediante a través de una columna NH_2, eluyendo con 5% metanol en DCM, para producir el compuesto deseado (35 mg), con una pureza calculada de 85%. ^{1}H NMR δ ($CDCl_3$): 1.26 (d, 3H), 2.28 (quintete, 2H), 2.49 (s, 3H), 3.33 (s, 3H), 3.41 - 3.54 (m, 2H), 4.18 (t, 2H), 4.50 - 4.58 (m, 1H), 4.64 (t, 2H), 6.77 (s, 1H), 7.08 (s, 1H), 7.25 (s, 1H), 7.31 (d, 1H), 8.04 (d, 1H), 8.07 (s, 1H), 8.26 (d, 1H), 8.30 (s, 1H), 9.46 (s, 1H); *m/z* 478 $(M+H)^+$.

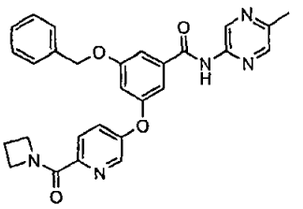
La preparación de 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-hidroxi-*N*-(5-metilpirazin-2-il)benzamida se describe a continuación.

3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-hidroxi-*N*-(5-metilpirazin-2-il)benzamida



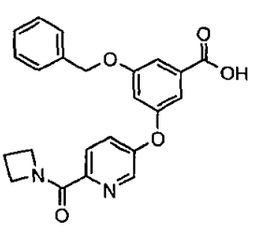
3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(5-metilpirazin-2-il)-5-[(fenilmetil)oxi]benzamida (3.9 g, 7.9 mmol) se disolvió en acetato de etilo (200 mL) y etanol (200 mL), luego se agregó 10% paladio sobre carbón vegetal. La reacción se agitó bajo una atmósfera de hidrógeno durante 16 horas. Se agregó metanol (150 mL) para ayudar a la solubilización del material y la suspensión se filtró, el residuo se tomó en DMF, se filtró y los filtrados combinados se evaporaron a sequedad para producir el material deseado (3.17 g). ^{1}H NMR δ (d_6-DMSO): 2.33 (quintete, 2H), 2.53 (s, 3H), 4.13 (t, 2H), 4.64 (t, 2H), 6.81 (s, 1H), 7.31 (s, 1H), 7.34 (s, 1H), 7.62 (d, 1H), 8.05 (d, 1H), 8.40 (s, 1H), 8.47 (s, 1H), 9.26 (s, 1H), 10.35 (s, 1H), 11.02 (s, 1H); *m/z* 406 $(M+H)^+$.

3-{[6-(Azetidin-1-ilcarbonil)piridin-3-il]oxi}-*N*-(5-metilpirazin-2-il)-5-[(fenilmetil)oxilbenzamida



1-Cloro-*N*,*N*,2-trimetil-1-propenilamina (2.67 mL, 20 mmol) se agregó a una solución de ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(fenilmetil)oxi]benzoico (6.18 g, 15.3 mmol) en DCM (100 mL) y la reacción se agitó a temperatura de la sala durante 50minutos. Se agregaron 2-amino-5-metilpirazina (3.34 g, 30.6 mmol) y piridina (2.5 mL, 30.6 mmol), y la reacción se agitó de un día para otro. El disolvente se retiró *in vacuo*, y el residuo se tomó en acetato de etilo (350 mL). La fase orgánica se lavó con agua (2 x 100 mL), salmuera (100 mL), se secó ($MgSO_4$), se filtró, y se evaporó *in vacuo*. El residuo se cromatografió en sílice, eluyendo con una gradiente de 50-75% acetato de etilo en isohexano, para producir el material deseado (4.01 g). ^{1}H NMR δ ($CDCl_3$): 2.28 (quintete, 2H), 2.49 (s, 3H), 4.18 (t, 2H), 4.63 (t, 2H), 5.05 (s, 2H), 6.78 (s, 1H), 7.10 (s, 1H), 7.25 - 7.37 (m, 7H), 8.04 (d, 1H), 8.07 (s, 1H), 8.25 (s, 2H), 9.46 (s, 1H); *m/z* 496 $(M+H)^+$.

Ácido 3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(fenilmetil)oxi]benzoico



Una mezcla de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato (5.16 g, 20 mmol), 2-(azetidin-1-ilcarbonil)-5-bromopiridina (5.3 g, 22 mmol), carbonato de cesio (19.56 g, 60 mmol) y bromotris(trifenilfosfina)cobre (3.73 g, 4 mmol) en DMA (100 mL) se agitó a 160°C durante 6 horas en un reactor microondas. El DMA se evaporó bajo presión reducida y el residuo

se disolvió en agua (200 mL) y se lavó con acetato de etilo (3 x 50 mL). La capa acuosa se acidificó con 2N ácido clorhídrico y se extrajo con acetato de etilo (3 x 100 mL), los orgánicos combinados se lavaron con agua (2 x 20 mL), salmuera (20 mL), se secaron ($MgSO_4$), se filtraron, y el disolvente se retiró *in vacuo* para producir el material deseado (6.18 g). ^{1}H NMR δ ($CDCl_3$): 2.29 (s, 2H), 4.20 (s, 2H), 4.64 (s, 2H), 5.04 (s, 2H), 6.83 (s, 1H), 7.22 - 7.44 (m, 7H), 7.49 (s, 1H), 7.79 - 8.63 (m, 2H); *m/z* 405 $(M+H)^+$.

Las preparaciones de metil 3-hidroxi-5-{[fenilmetil]oxi}benzoato y 2-(azetidin-1-ilcarbonil)-5-bromopiridina se describieron anteriormente.

BIOLÓGICA

Pruebas:

Los efectos biológicos de los compuestos de fórmula (I) pueden analizarse en la siguiente forma:

(I) Actividad Enzimática

La actividad enzimática de la GLK pancreática humana recombinante puede medirse incubando GLK, ATP y glucosa. La velocidad de formación de producto puede determinarse acoplando el análisis a una G-6-P dehidrogenasa, sistema NADP/NADPH y midiendo el aumento lineal con el tiempo de la densidad óptica a 340nm (Matschinsky *et al.*, 1993). La activación de GLK por los compuestos puede evaluarse utilizando este análisis en la presencia o ausencia de GLKRP como se describe en Brocklehurst *et al.*, (Diabetes 2004, **53**, 535-541).

Producción de GLK recombinante y GLKRP

GLK humana y cADN GLKRP se obtuvieron por PCR de mARN hepático y pancreático humanos respectivamente, usando técnicas establecidas descritas en Sambrook J, Fritsch EF & Maniais T, 1989. Los cebadores de PCR se diseñaron de acuerdo con las secuencias de GLK y

cADN GLKRP mostradas en Tanizawa *et al.,* 1991 y Bonthron, D.T *et al.,* 1994 (corregidas más tarde en Warner, J.P. 1995).

Clonación en vectores Bluescript II

GLK y cADN GLKRP se clonaron en *E. coli* usando pBluescript II, (Short *et al.,* 1998) un vector de clonación recombinante similar al empleado por Yanisch-Perron C *et al.,* (1985), que comprendía un replicón a base de colEI con un fragmento de ADN poli-enlazador que contenía múltiples sitio de restricción única, flanqueados por secuencias promotoras T3 y T7 de bacteriófago; un origen de fago filamentoso de replicación y un gen marcador de resistencia al medicamento ampicilina.

Transformaciones

Las transformaciones de *E. coli* se llevaron generalmente a cabo por electroporación. Cultivos de 400 mL de cepas DH5a o BL21 (DE3) se cultivaron en caldo L a un OD 600 de 0.5 y se cosecharon por centrifugación a 2.000g. Las células se lavaron dos veces en agua desionizada helada, se resuspendieron en 1mL 10% glicerol y se almacenaron en alícuotas a -70°C. Las mezclas de ligación se desalinizaron usando membranas Millipore V series™ (0.0025mm tamaño del poro). 40mL de células se incubaron con 1mL de mezcla de ligación o ADN de plásmido en hielo durante 10 minutos en tubos de laboratorio de electroporación de 0.2cm, y luego se pulsaron usando un aparato Gene Pulser™ (BioRad) a 0.5kVcm^{-1}, 250mF. Se transformaron los transformantes en L-agar suplementado con tetraciclina a 10mg/mL o ampicilina a 100mg/mL.

Expresión

GLK se expresó a partir del vector pTB375NBSE en células BL21 de de *E. coli*, produciendo una proteína recombinante que contenía un marcador 6-His inmediatamente adyacente a la metionina N-terminal. Alternativamente, otro vector apropiado es pET21(+)DNA, Novagen,

número de Catálogo 697703. El marcador 6-His se usó para permitir la purificación de la proteína recombinante en una columna empacada con níquel-ácido nitrilotriacético agarosa adquirido de Qiagen (número de Catálogo 30250).

GLKRP se expresó a partir del vector pFLAG CTC (IBI Kodak) en células BL21 de *E. coli*, produciendo una proteína recombinante que contenía un marcador FLAG C-terminal. La proteína se purificó inicialmente por intercambio iónico DEAE Sefarosa, seguido por utilización del marcador FLAG para purificación final en una columna de inmunoafinidad M2 anti-FLAG adquirida de Sigma-Aldrich (número de Catálogo A1205).

(2) Prueba de Tolerancia a la Glucosa Oral (OGTT)

Las pruebas de tolerancia a la glucosa oral se realizaron en ratas fa/fa obesas Zucker conscientes (12-13 semanas de edad o más) alimentadas con una dieta alta en grasa (45 % kcal grasa) durante un mínimo de dos semanas antes de la experimentación. Se privó a los animales de comida durante 2 horas antes de usarlos para los experimentos. Un compuesto de prueba o un vehículo se les dio oralmente 120 minutos antes de la administración oral de una solución de glucosa en una dosis de 2 g/kg de peso corporal. Se midieron los niveles de glucosa sanguínea usando un medidor de glucosa Accucheck de muestras de sangrado de la cola tomadas en puntos de tiempo diferentes antes y después de la administración de glucosa (tiempo transcurrido 60 minutos). Se generó una curva de tiempo de los niveles de glucosa sanguínea y se calculó el área bajo la curva (AUC) durante 120 minutos (siendo ceto el tiempo de administración de la glucosa). Se determinó la inhibición porcentual usando al AUC en el grupo vehículo - control como inhibición porcentual cero.

Por lo general los compuestos de la invención poseen una actividad activadora de glucocinasa con una EC_{50} de menos de alrededor de 500nM. Por ejemplo, el Ejemplo 3 tiene una EC_{50} de 31nm.

Ejemplo 3 exhibe 54% de actividad OGTT a 10mg/kg.

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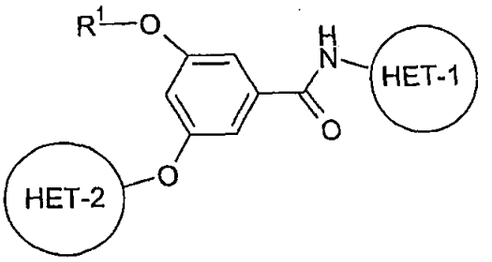
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Reivindicaciones:

1. Un compuesto de fórmula (I):



(I)

en donde:

R^1 se selecciona de isopropilo, but-2-ilo, ciclopentilo, 1,1,1-trifluoroprop-2-ilo, 1,3-difluoroprop-2-ilo, but-1-in-3-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-hidroxibut-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-metoxiprop-2-ilo, 1-metoxibut-2-ilo, 2- hidroxiprop-1-ilo, 2-metoxiprop-1-ilo, 2-hidroxibut-1-ilo, 2-metoxibut-1-ilo, 1- fluorometoxiprop-2-ilo, 1,1-difluorometoxiprop-2-ilo y 1-trifluorometoxiprop-2-ilo;

HET-1 es un anillo heteroarilo enlazado a C, de 5 ó 6 miembros, que contiene un átomo de nitrógeno en la posición 2 y, de manera opcional, 1 ó 2 heteroátomos de anillo adicionales, seleccionados independientemente de O, N y S; anillo que se sustituye opcionalmente en cualquier átomo de nitrógeno (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^7 y/o en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^6;

HET-2 es un anillo heteroarilo de 5 ó 6 miembros, que contiene 1, 2 ó 3 hetereoátomos de anillo seleccionados independientemente de O, S y N; anillo que se sustituye en un átomo de carbono disponible por un sustituyente seleccionado de R^2, y se sustituye además opcionalmente en 1 ó 2 átomos de carbono disponibles por un sustituyente independientemente seleccionado de R^3 y/o en un átomo de nitrógeno disponible (siempre que, con ello, no se cuaternice) por un sustituyente seleccionado de R^{10};

R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;

R^3 se selecciona de metilo, trifluorometilo y halo;

R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, de 4 a 7 miembros, que contiene opcionalmente 1 ó 2 heteroátomos adicionales (aparte del átomo N enlazante) seleccionados independientemente de O, N y S, en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)-, y en donde un átomo de azufre en el anillo puede oxidarse opcionalmente en un grupo S(O) o $S(O)_2$; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 ó 2 sustituyentes seleccionados independientemente de R^8 y/o en un átomo de nitrógeno disponible por un sustituyente seleccionado de R^9; o R^4 y R^5, junto con el átomo de nitrógeno al cual se unen, forman un anillo heterocíclico saturado o parcialmente insaturado, bicíclico, de 6-10 miembros, que contiene opcionalmente 1 átomo de nitrógeno adicional (aparte del átomo N enlazante), en donde un grupo $-CH_2-$ puede reemplazarse opcionalmente por un grupo -C(O)-; anillo que se sustituye opcionalmente en un átomo de carbono disponible por 1 sustituyente seleccionado de hidroxi y R^3 o en un átomo de nitrógeno disponible por metilo;

R^6 se selecciona independientemente de (1-4C)alquilo, halo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo;

R^7 se selecciona independientemente de (1-4C)alquilo, halo(1-4C)alquilo, dihalo(1-4C)alquilo, trihalo(1-4C)alquilo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, (1-4C)alquilS(O)p(1-4C)alquilo, amino(1-4C)alquilo, (1-4C)alquilamino(1-4C)alquilo y di(1-4C)alquilamino(1-4C)alquilo;

R^8 se selecciona de hidroxi, (1-4C)alcoxi, (1-4C)alquilo, aminocarbonilo, (1-4C)alquilaminocarbonilo, di(1-4C)alquilaminocarbonilo, (1-4C)alquilamino, di(1-4C)alquilamino, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquilo y -S(O)p(1-4C)alquilo;

R^9 se selecciona de (1-4C)alquilo, -C(O)(1-4C)alquilo, aminocarbonilo, (1-4C) alquilaminocarbonilo, di(1-4C)alquilaminocarbonilo, (1-4C)alcoxi(1-4C)alquilo, hidroxi(1-4C)alquil y -S(O)p(1-4C)alquilo;
R^{10} se selecciona de (1-4C)alquilo, (3-6C)cicloalquilo, hidroxi(1-4C)alquilo, (1-4C)alcoxi(1-4C)alquilo, -C(O)(1-4C)alquilo, bencilo, y (1-4C)alquilsulfonilo;
p es (independientemente de cada ocurrencia) 0, 1 ó 2;
o su sal.

2. Un compuesto de la fórmula (I), como se reivindica en la reivindicación 1, o su sal en donde R^1 es de la sub-fórmula X:



(X)

en donde R^x se selecciona de metilo, etilo, trifluorometilo, etinilo, hidroximetilo, hidroxietilo, metoximetilo, fluorometoximetilo, difluorometoximetilo y trifluorometoximetilo.

3. Un compuesto de la fórmula (I), como se reivindica en la reivindicación 1 o la reivindicación 2, o su sal, en donde R^2 es $-CONR^4R^5$.

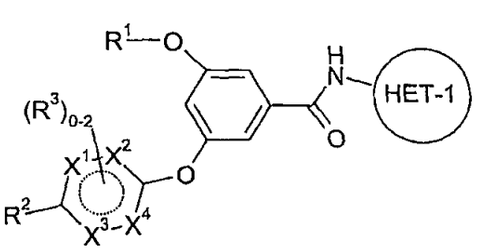
4. Un compuesto de la fórmula (I), como se reivindica en la reivindicación 1, o su sal, en donde: R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;
HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo, piridilo, isoxazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo y/o (en un átomo de carbono) por fluoro;
HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;

R^3 es metilo, fluoro o cloro;
R^2 se selecciona de $-C(O)NR^4R^5$ y $-SO_2NR^4R^5$;
R^4 y R^5 juntos forman un anillo azetidinilo, 7-azabiciclo[2.2.1]hept-7-ilo, morfolino, o pirrolidinilo.

5. Un compuesto de la fórmula (I) como se reivindica en la reivindicación 1 o su sal, en donde:
R^1 se selecciona de isopropilo, ciclopentilo, 1,3-difluoroprop-2-ilo, but-2-ilo, 1-hidroxiprop-2-ilo, 2-hidroxibut-3-ilo, 1-difluorometoxiprop-2-ilo, tetrahidrofurilo, tetrahidropiranilo, 1-hidroxibut-2-ilo y 1-metoxiprop-2-ilo;
HET-1 se selecciona de tiazolilo, pirazolilo, tiadiazolilo, piridilo, isoxazolilo y pirazinilo, en donde R^1 se sustituye opcionalmente con un grupo metilo, isopropilo o etilo y/o (en un átomo de carbono) por fluoro;
HET-2 se selecciona de piridilo, pirazinilo, piridazinilo, tiazolilo y pirimidinilo, sustituido por R^2 y sustituido opcionalmente por R^3;
R^3 es metilo, fluoro o cloro;
R^2 es $-CONR^4R^5$;
R^4 y R^5 juntos forman un anillo azetidinilo o pirrolidinilo.

6. Un compuesto de la fórmula (I), como se reivindica en una cualquiera de las reivindicaciones 1 a 5, o su sal, en donde R^4 y R^5 juntos forman un anillo azetidinilo.

7. Un compuesto de la fórmula (I), como se reivindica en una cualquiera de las reivindicaciones 1 a 6, que es un compuesto de fórmula (IA), o su sal:



(IA)

en donde cada uno de X^1, X^2 y X^3 se selecciona independientemente de CH, N, S y O; X^4 está ausente (para conformar un anillo de 5 miembros) o se selecciona de CH, N, O y S;
siempre que por lo menos uno de X^1, X^2, X^3 y X^4 sea CH y siempre que no haya enlaces O-O, O-S o S-S en el anillo.

8. Un compuesto de la fórmula (I), como se reivindica en la reivindicación 1, que es uno o más de los siguientes:
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H- pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil) oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-1,3-tiazol-2-ilbenzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H- pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[5-(azetidin-1-ilsulfonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-[(1-metiletil) oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[3-cloro-5-(morfolin-4-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida; y
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida; y/o
3-{[5-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metilpropil] oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[2-(azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[2-(azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-({(1S)-2-[(difluorometil)oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il) benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il) benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1R,2R)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S,2S)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[4-(azetidin-1-ilcarbonil)- 1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[4-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-[(1-metiletil) oxi]-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-(hidroximetil)propil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida; y/o
3-{[2-(azetidin-1-ilcarbonil)pirimidin-5-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-(ciclopentiloxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il] oxi} -5 -(ciclopentiloxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-(ciclopentiloxi)-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1R,2R)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S,2S)-2-hidroxi-1-metilpropil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[4-(azetidin-1-ilcarbonil)-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1,3-tiazol-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-piridin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(1-metiletil)oxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(1-metiletil)oxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(1-metiletil)oxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-piridin-2-ilbenzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-isoxazol-3-il-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(1-metiletil)oxi]-N-1H-pirazol-3-ilbenzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil) oxi]-N-1H-pirazol-3-ilbenzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1,5-dimetil-1H-pirazol-3-il)-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;

3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1,5-dimetil-1H-pirazol-3-il)-5-{[2-fluoro-1-(fluorometil)etil]oxi}benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridazin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(1-metil-1H-pirazol-3-il)benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(4-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-1H-pirazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1,5-dimetil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(4-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(5-metil-1,3-tiazol-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-etil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-[1-(1-metiletil)-1H-pirazol-3-il]-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida; 3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-1H-pirazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-metilpirazin-2-il)-5 -[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-fluoropiridin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[3-cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-(5-metilpirazin-2-il)benzamida;
3-{[5-cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[3-cloro-5-(pirrolidin-1-ilcarbonil)piridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-metilpirazin-2-il)-5-(tetrahidro-2H-piran-4-iloxi)benzamida; y
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3R)-tetrahidrofuran-3-iloxi]benzamida; y/o
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-isoxazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-pirazin-2-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-(5-fluoropiridin-2-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-piridin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-isoxazol-3-il-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(4-metil-1,3-tiazol-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metil-1,3-tiazol-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-pirazin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-[(1-metiletil)oxi]-N-pirazin-2-ilbenzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi) etil]oxi}-N-pirazin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-[(1-metiletil)oxi]-N-pirazin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-pirazin-2-ilbenzamida;
3-{[3-cloro-5-(morfolin-4-ilcarbonil)piridin-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(7-azabiciclo[2.2.1]hept-7-ilcarbonil)-3-cloropiridin-2-il]oxi}-N-(1-metil-1H- pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida; y
3-{[5-(azetidin-1-ilcarbonil)-4-metil-1,3-tiazol-2-il]oxi}-N-(1-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida; y/o
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi} -5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-pirazin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil]oxi}-N-piridin-2-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)piridin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil] oxi}-N-(3-metil-1,2,4-tiadiazol-5-il)benzamida;
N-(1-metil-1H-pirazol-3-il)-3-{[6-(pirrolidin-1-ilcarbonil)piridin-3-il]oxi}-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-pirazin-2-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-(5-metil-1H-pirazol-3-il)-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;

3-{[6-(azetidin-1-ilcarbonil)piridin-3-il] oxi}-N-1H-pirazol-3-il-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)-3-cloropiridin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil)etil]oxi}-N-(5-metil-1H-pirazol-3-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil) etil]oxi}-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[2-fluoro-1-(fluorometil) etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1S)-2-hidroxi-1-metiletil] oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-({(1S)-2-[(difluorometil) oxi]-1-metiletil}oxi)-N-1H-pirazol-3-ilbenzamida;
3-{[5-(azetidin-1-ilsulfonil)-4-metil-1,3-tiazol-2-il]oxi}-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-[1-(difluorometil)-1H-pirazol-3-il]-5-[(3S)-tetrahidrofuran-3-iloxi]benzamida;
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-N-[1-(difluorometil)-1H-pirazol-3-il]-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-N-[1-(difluorometil)-1H-pirazol-3-il]-5-{[(1S)-1-metil-2-(metiloxi)etil]oxi}benzamida; y/o
3-{[5-(azetidin-1-ilcarbonil)pirazin-2-il]oxi}-5-{[(1*R*)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
3-{[6-(azetidin-1-ilcarbonil)piridin-3-il]oxi}-5-{[(1R)-1-metil-2-(metiloxi)etil]oxi}-N-(5-metilpirazin-2-il)benzamida;
o su sal.

9. Una composición farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8, o su sal

farmacéuticamente aceptable, junto con un diluente o sustancia portadora farmacéuticamente aceptable.

10. Un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8, o su sal farmacéuticamente aceptable para uso como un medicamento.

11. Un compuesto de acuerdo con la reivindicación 10, en donde el medicamento es un medicamento para el tratamiento de una enfermedad mediada por GLK, en particular diabetes tipo 2.

12. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8, o su sal farmacéuticamente aceptable, en la preparación de un medicamento para el tratamiento de una enfermedad mediada por GLK.

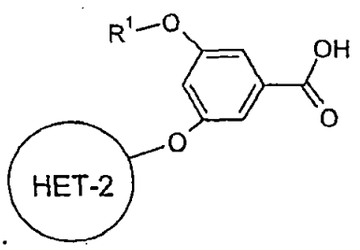
13. El uso de un compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 8, o su sal farmacéuticamente aceptable, en la preparación de un medicamento para el tratamiento de diabetes tipo 2.

14. Un método de tratar enfermedades mediadas por GLK, administrando una cantidad efectiva de un compuesto de fórmula (I) o (IA), como se reivindica en una cualquiera de las reivindicaciones 1 a 8, o su sal farmacéuticamente aceptable, a un mamífero necesitado de tal tratamiento.

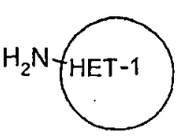
15. El método de la reivindicación 14 en donde la enfermedad mediada por GLK es diabetes tipo 2.

16. Un proceso para la preparación un compuesto de fórmula (I) o (IA), como se reivindica en una cualquiera de las reivindicaciones 1 a 8, el cual comprende un proceso a) a e) (en donde las variables son como se definen para los compuestos de fórmula (I) en la reivindicación 1, a menos que se especifique lo contrario):

(a) Reacción de un ácido de Fórmula (III) o su derivado activado con un compuesto de Fórmula (IV), en donde R^1 es como se define anteriormente, o su versión protegida;



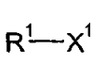
(III)



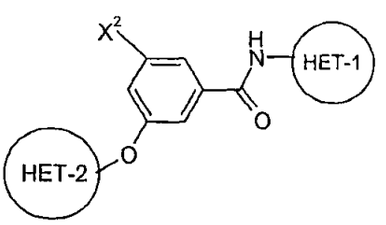
(IV);

o

(b) reacción de un compuesto de Fórmula (V) con un compuesto de Fórmula (VI),



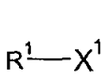
(V)



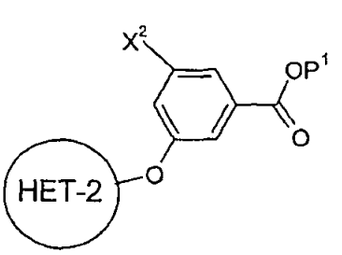
(VI)

en donde X^1 es un grupo saliente y X^2 es un grupo hidroxilo o X^1 es un grupo hidroxilo y X^2 es un grupo saliente, y en donde R^1 es como se define anteriormente, o su versión protegida;

proceso (b) podría llevarse igualmente usando el éster intermedio de Fórmula (VII), en donde P^1 es un grupo protector como de describe más adelante, seguido por hidrólisis del éster y formación de amida mediante procedimientos descritos en alguna otra parte y bien conocidos por los expertos en el arte;



(V)

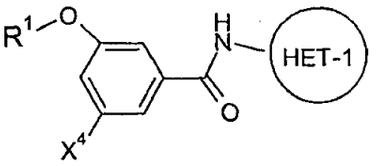


(VII)

o

(c) reacción de un compuesto de Fórmula (VIII) con un compuesto de Fórmula (IX)

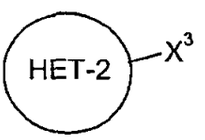


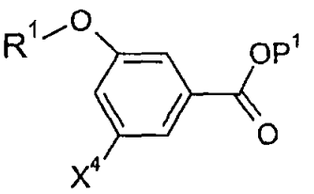


(VIII) (IX)

en donde X^3 es un grupo saliente o un reactivo organometálico y X^4 es un grupo hidroxilo o X^3 es un grupo hidroxilo y X^4 es un grupo saliente o un reactivo organometálico, y en donde R^1 es como se define anteriormente, o su versión protegida;

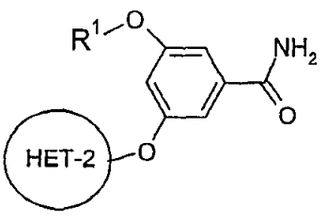
proceso (c) podría llevarse también a cabo usando el éster intermedio de Fórmula (X), seguido por hidrólisis de éster y formación de amida por procedimientos descritos en alguna otra parte y bien conocidos por los expertos en el arte;

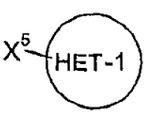




(VIII) (X)

(d) reacción de un compuesto de Fórmula (XI) con un compuesto de Fórmula (XII),

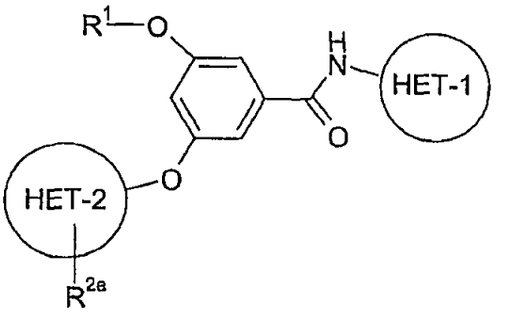




(XI) (XII);

en donde X^5 es un grupo saliente; y en donde R^1 es como se define anteriormente, o su versión protegida; o

e) reacción de un compuesto de fórmula (XIII)



(XIII)

en donde R^{2a} es un precursor de R^2, tal como un ácido carboxílico, éster o anhídrido (para R^2 = -$CONR^4R^5$) o los equivalentes de ácido sulfónico (para R^2 es -$SO^2NR^4R^5$); con una amina de la fórmula -NR^4R^5;

y, posteriormente, si es necesario:

i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

ii) retirar cualesquiera grupos protectores; y/o

iii) formar una sal del mismo.

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)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	101901-1 WO
I	Title of Invention	CHEMICAL COMPOUNDS

II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	AP: (BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LT LU LV MC NL PL PT RO SE SI SK TR); OA: (BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG); AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KN KP KR KZ LC LK LR LS LT LU LV LY MA MD MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address	SE-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
II-10	e-mail	patents@astrazeneca.com
III-1	Applicant and/or inventor	
III-1-1	This person is	applicant only
III-1-2	Applicant for	MG
III-1-4	Name	ASTRAZENECA UK LIMITED
III-1-5	Address	15 Stanhope Gate London Greater London W1K 1LN United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB

III-2	**Applicant and/or Inventor**	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	MCKERRECHER, Darren
III-2-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-2-6	State of nationality	GB
III-2-7	State of residence	GB
III-3	**Applicant and/or Inventor**	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	PIKE, Kurt, Gordon
III-3-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB
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)	WARING, Michael, James
III-4-5	Address	AstraZeneca R&D Alderley Alderley Park Macclesfield Cheshire SK10 4TG United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB

IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	GLOBAL INTELLECTUAL PROPERTY
IV-1-2	Address	AstraZeneca AB SE-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	09 July 2005 (09.07.2005)
VI-1-2	Number	0514173.4
VI-1-3	Country	GB
VI-2	**Priority claim of earlier national application**	
VI-2-1	Filing date	09 August 2005 (09.08.2005)
VI-2-2	Number	0516297.9
VI-2-3	Country	GB
VI-3	**Priority claim of earlier national application**	
VI-3-1	Filing date	24 November 2005 (24.11.2005)
VI-3-2	Number	0523862.1
VI-3-3	Country	GB
VI-4	**Priority claim of earlier national application**	
VI-4-1	Filing date	02 December 2005 (02.12.2005)
VI-4-2	Number	0524589.9
VI-4-3	Country	GB

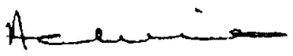
PCT REQUEST

Original (for **SUBMISSION**)

VI-5	**Priority claim of earlier national application**		
VI-5-1	Filing date	22 April 2006 (22.04.2006)	
VI-5-2	Number	0607977.6	
VI-5-3	Country	GB	
VII-1	**International Searching Authority Chosen**	European Patent Office (EPO) (ISA/EP)	
VIII	**Declarations**	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	**Check list**	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	6	✓
IX-2	Description	248	-
IX-3	Claims	17	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	272	
	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. AZAB/MAY06/011	-
IX-11	Copy of general power of attorney	reference no. AZUK/MAY06/011	-
IX-13	Priority document(s)	Item(s) VI-1 VI-2 VI-3 VI-4 VI-5	-
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	

PCT REQUEST

Original (for **SUBMISSION**)

X-1	Signature of applicant, agent or common representative	
X-1-1	Name	GLOBAL INTELLECTUAL PROPERTY
X-1-2	Name of signatory	WILLIAMS, Anne Rachel Burton
X-1-3	Capacity	Agent

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

AS: 105900

BE IT KNOWN that I, STEPHEN DAVID FINN of 31 Amersham Hill Drive, High Wycombe, Buckinghamshire, United Kingdom, a duly authorised Notary Public

CERTIFY ONLY that Blair Consular Services Limited on behalf of their client

AstraZeneca AB

have this day presented to me the hereto annexed document describing itself as an

ASSIGNMENT/TRASPASO signed by MCKERRECHER Darren, PIKE Kurt, Gordon and WARING Michael, James

and that the said Blair Consular Services Limited have represented to me by such presentation that their said client has represented to them that the said annexed document is an authentic original document.

SIGNED AND SEALED at 31 Amersham Hill Drive, High Wycombe, Buckinghamshire, United Kingdom on 7th December 2007.

Stephen Finn
Notary Public

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 / a été signé par: **Stephen David Finn**

3. Acting in the capacity of / agissant en qualité de: **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de: **The Said Notary Public**

5. at London/à Londres

   Certified/Attesté
6. the/le **11 December 2007**

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 **H615562**

9. Stamp: / timbre:

10. Signature: **J Steven**

FOREIGN AND COMMONWEALTH OFFICE LONDON

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

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

ASSIGNMENT

The undersigned,

MCKERRECHER Darren, PIKE Kurt, Gordon and WARING Michael, James

domiciled in

AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom

hereby state under oath to be the sole and true inventors of

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

HETEROARYL BENZAMIDE DERIVATIVES FOR USE AS GLK ACTIVATORS IN THE TREATMENT OF DIABETES

We state as well that we assign, without reservations or limitation, in favor of

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

a corporation organized and existing under the laws of Sweden

domiciled in

SE-151 85 Södertälje, Sweden

organizada y existente de conformidad con la leves de

domiciliada en

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

MCKERRECHER Darren

PIKE Kurt, Gordon

WARING Michael, James

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.

NOTARY PUBLIC (Notario Público)

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 mi 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.

TRADUCCION AL ESPAÑOL del Documento de Cesión a **AstraZeneca AB** firmado por los cedentes y el cesionario.

TENGASE POR SABIDO QUE YO, STEPHEN FINN, de 31 Amersham Hill Drive, High Wycombe, Buckinghamshire, Reino Unido, un notario público debidamente autorizado

CERTIFICO SOLAMENTE que Blair Consular Services Limited a nombre de su cliente:

AstraZeneca AB

ha presentado ante mi este día el documento anexo al presente describiéndolo como:

CESION/TRASPASO firmada por MCKERRECHER Darren, PIKE Kurt, Gordon y WARING Michael, James

y que dicho Blair Consular Services Limited ha presentado ante mi tal certificación de que su cliente les ha confirmado que el dicho documento anexo es un documento original auténtico.

FIRMADO Y SELLADO en 31 Amersham Hill Drive, High Wycombe, Buckinghamshire, Reino Unido el 7 de diciembre de 2007.

STEPHEN FINN
NOTARIO PUBLICO

APOSTILLA

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

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

   Este documento público

2. ha sido firmado por **Stephen David Finn**
3. Actuando en capacidad de **Notario Público**
4. lleva el sello/timbre de **Dicho Notario Público**

Certificado

5. en Londres 6. el **11 de Diciembre de 2007**
7. por el Secretario Principal de Estado de Su Majestad para Relaciones Exteriores y de la Mancomunidad
8. No. **H615562**
9. Sello/Timbre 10. Firma: **J. Steven**

Por el Secretario de Estado

Si este documento ha de ser utilizado en un país el cual no es parte de la Convención de La Haya del 5 de octubre de 1961, debe ser presentado ante la sección consular de la misión que representa ese país. Una apostilla o certificado de legalización solo confirma que la firma, sello o timbre en el documento es genuino. No significa que los contenidos del documento estén correctos o que la Oficina Extranjera y de la Mancomunidad apruebe sus contenidos.

Brigard & Castro

BOGOTA - COLOMBIA

PODER

Yo (nosotros),

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE** y/o **JUAN PABLO CADENA SARMIENTO** y/o **BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre

Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151 Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions; such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or explotation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models, in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, 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 2003 of
personally appeared before me
KEVIN BILL
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of
under date of 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.

2

885

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**

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

Como constar que esta copia, coincide con documento original presentado para su autenticación. Republica de Colombia D.C. 24 JUL 2007 BEATRIZ S. NAVARRO NOTARIA 16

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.

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TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el **Poder** concedido por **ASTRAZENECA AB**, domiciliada en SE - 151 Sodertalje, Suecia a **Ramiro Castro Duque** y/o **Juan Pablo Cadena Sarmiento** y/o **Beatriz Jaramillo S**, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.

AUTENTICACIÓN

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

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
   ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

CERTIFICADO

5. en Londres 6. el **17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello 10. Firma



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 065

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 e/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 e/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

Fecha de la defunción											Hora	Número de certificado de defunción
Año	2	0	0	4	Mes	1	0	Día	3	0	04:10 PM	A- 2094375.

Juzgado que profirió la sentencia — Presunción de muerte — 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 LEOLA VALLEJO RESTREPO NOTARIA 32

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

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 5562247, que expido en la ciudad de Bogotá D C, hoy 17 NOV. 2004

NOTARIA 32 DEL CIRCULO
DE BOGOTA D C
NELSON FLOREZ
SECRETARIO DELEGADO

NELSON FLOREZ
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1534 DE 1996

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-001120- -00000-0000

Fecha: 2008-01-08 16:10:11 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 590

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 Neva Cortes

Firma 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

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 592

2020
Bogotá D.C.,

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA	Radicación No.	8 1120
	Solicitud internacional	PCT/GB2006/002471
	Fecha inicio fase nacional	09/02/2008
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5516
	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, 20 FEB. 2008

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

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