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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

PCT
SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No.

04-22003

54 TITULO COMPUESTOS QUE AFECTAN LA GLUCOCINASA

51 CLASIFICACION INTERNACIONAL

A61K 31/425

71 SOLICITANTE

ASTRAZENECA AB

DOMICILIO

SODERTALJE SUECIA

74 APODERADO

RAMIRO CASTRO DUQUE

22 SANTAFE DE BOGOTA, D.C.

Q.F.

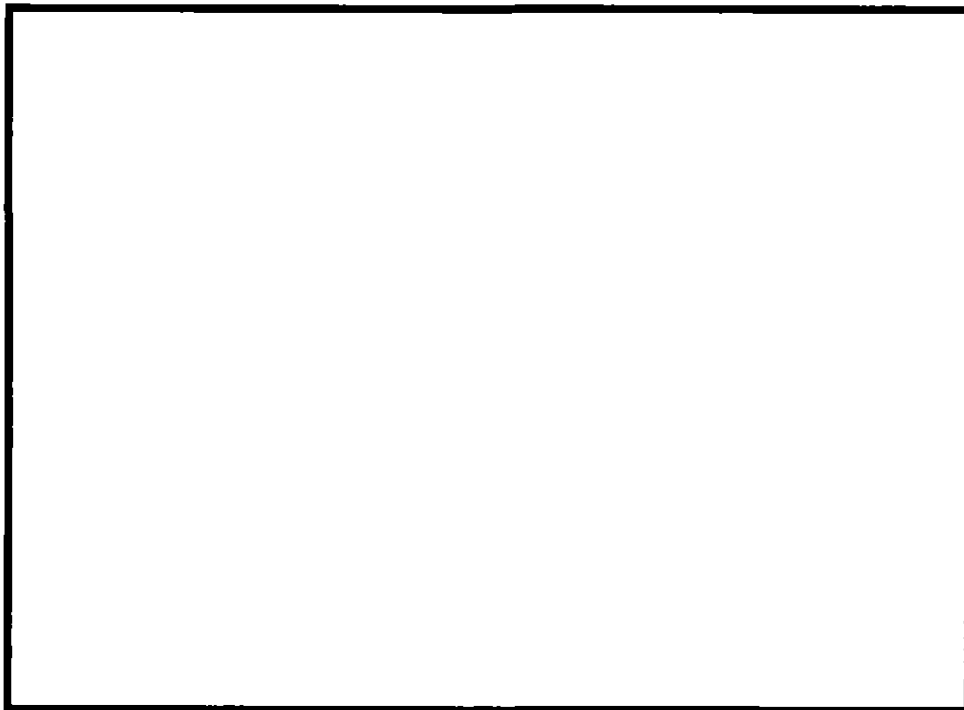
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar 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.
- ☐ Arie 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.
- ☒ Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12. Solicito la concesión de la patente:

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá, T.P. 1003 del C.S.J.

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

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	Vr. PAGO
BRIARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21589772	20/01/2004	12,762,000.00

***** CONCEPTO *****

CANT. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	\$ 422,000.00

SOM: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PCT

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

- 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.*

c1ccc(cc1C(=O)N)C(*)

(D)

(57) Abstract: The invention relates to the use of a compound of Formula (I) or a salt, solvate or prodrug thereof, wherein R¹, R², R³, n and m are as described in the specification, in the preparation of a medicament for the treatment or prevention of a disease condition mediated through glucokinase (GLK), such as type 2 diabetes. The invention also relates to a novel group of compounds of Formula (I) and to methods for preparing compounds of Formula (I).

WO 03/015774 A1

COMPOUNDS EFFECTING GLUCOKINASE

The present invention relates to the use of a group of benzamide compounds in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through glucokinase (GLK), 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 benzamide compound, a sub-group of novel compounds of said benzamide compounds, and the use of such a compound in the conditions described above.

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) K_m 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, Type 2 maturity-onset diabetes of the young (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, 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

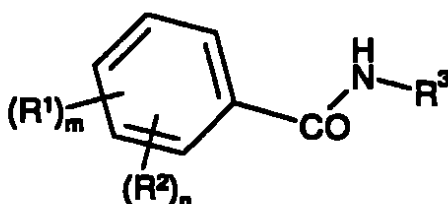
mediated through a fructose induced increase in cytosolic GLK activity in the hepatocyte by the mechanism described below [13].

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 elevated 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 exclusively 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 exclusively 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 and 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).

- In WO0058293 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 in Example A. Compounds of the present invention may activate GLK directly or may activate GLK by inhibiting the interaction of GLKRP with GLK. The latter mechanism offers an important advantage over direct activators of GLK in that they will not cause the severe hypoglycaemic episodes predicted after direct stimulation. Many compounds of the present invention may show favourable selectivity compared to known GLK activators.
- WO9622282, WO9622293, WO9622294, WO9622295, WO9749707 and WO9749708 disclose a number of intermediates used in the preparation of compounds useful as vasopressin agents which are structurally similar to those disclosed in the present invention. Structurally similar compounds are also disclosed in WO9641795 and JP8143565 (vasopressin antagonism), in JP8301760 (skin damage prevention) and in EP619116 (osetopathy).
- WO01/12621 describes the preparation of as isoxazoly|pyrimidines and related compounds as inhibitors of cJUN N-terminal kinases, and pharmaceutical compositions containing such compounds.
- Cushman *et al* [Bioorg Med Chem Lett (1991) 1(4), 211-14] describe the synthesis of pyridine-containing stilbenes and amides and their evaluation as protein-tyrosine kinase inhibitors. Rogers *et al* [J Med Chem (1981) 24(11) 1284-7] describe mesoionic purinone analogs as inhibitors of cyclic-AMP phosphodiesterase.
- WO00/26202 describes the preparation of 2-amino-thiazole derivatives as antitumour agents. GB 2331748 describes the preparation of insecticidal thiazole derivatives.
- WO96/36619 describes the preparation of aminothiazole derivatives as ameliorating agents for digestive tract movements. US 5466715 and US 5258407 describe the preparation of 3,4-disubstituted phenol immunostimulants. JP 58069812 describes hypoglycemic pharmaceuticals containing benzamide derivatives. US 3950351 describes 2-benzamido-5-nitrothiazoles and Cavier *et al* [Eur J Med Chem - Chim Ther (1978) 13(6), 539-43] discuss the biological interest of these compounds.

We present as a feature of the invention the use of a compound of Formula (I) or a salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through GLK:



Formula (I)

wherein

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

and $n + m > 0$;

- each R^1 is independently selected from OH , $-(\text{CH}_2)_{1-4}\text{OH}$, $-\text{CH}_3-\text{F}_n$, $-(\text{CH}_2)_{1-4}\text{CH}_3-\text{F}_n$, $-\text{OCH}_3-\text{F}_n$, halo, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, NH_2 , $-\text{NH}-\text{C}_{1-4}\text{alkyl}$, $-\text{N}-\text{di}-(\text{C}_{1-4}\text{alkyl})$, CN , formyl, phenyl or heterocyclyl optionally substituted by $\text{C}_{1-6}\text{alkyl}$;

each R^2 is the group $\text{Y}-\text{X}-$

- wherein each X is a linker independently selected from:
- $-\text{O}-\text{Z}-$, $-\text{O}-\text{Z}-\text{O}-\text{Z}-$, $-\text{C}(\text{O})\text{O}-\text{Z}-$, $-\text{OC}(\text{O})-\text{Z}-$, $-\text{S}-\text{Z}-$, $-\text{SO}-\text{Z}-$, $-\text{SO}_2-\text{Z}-$, $-\text{N}(\text{R}^6)-\text{Z}-$, $-\text{N}(\text{R}^6)\text{SO}_2-\text{Z}-$, $-\text{SO}_2\text{N}(\text{R}^6)-\text{Z}-$, $-\text{CH}=\text{CH}-\text{Z}-$, $-\text{C}\equiv\text{C}-\text{Z}-$, $-\text{N}(\text{R}^6)\text{CO}-\text{Z}-$, $-\text{CON}(\text{R}^6)-\text{Z}-$, $-\text{C}(\text{O})\text{N}(\text{R}^6)\text{S}(\text{O})_2-\text{Z}-$, $-\text{S}(\text{O})_2\text{N}(\text{R}^6)\text{C}(\text{O})-\text{Z}-$, $-\text{C}(\text{O})-\text{Z}-$, $-\text{Z}-$, $-\text{C}(\text{O})-\text{Z}-\text{O}-\text{Z}-$, $-\text{N}(\text{R}^6)-\text{C}(\text{O})-\text{Z}-\text{O}-\text{Z}-$, $-\text{O}-\text{Z}-\text{N}(\text{R}^6)-\text{Z}-$, $-\text{O}-\text{C}(\text{O})-\text{Z}-\text{O}-\text{Z}-$ or a direct bond;

each Z is independently a direct bond, $\text{C}_{2-6}\text{alkenylene}$ or a group of the formula $-(\text{CH}_2)_p-\text{C}(\text{R}^{6a})_2-(\text{CH}_2)_q-$;

each Y is independently selected from $\text{aryl}-\text{Z}^1-$, $\text{heterocyclyl}-\text{Z}^1-$, $\text{C}_{3-7}\text{cycloalkyl}-\text{Z}^1-$, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, $-(\text{CH}_2)_{1-4}\text{CH}_3-\text{F}_n$ or $-\text{CH}(\text{OH})\text{CH}_3-\text{F}_n$; wherein

- each Y is independently optionally substituted by up to 3 R^4 groups;
- each R^4 is independently selected from halo, $-\text{CH}_3-\text{F}_n$, CN , NH_2 , $\text{C}_{1-6}\text{alkyl}$, $-\text{OC}_{1-6}\text{alkyl}$, $-\text{COOH}$, $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$, OH or phenyl optionally substituted by $\text{C}_{1-6}\text{alkyl}$ or $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$,

or R^5-X^1 , where X^1 is independently as defined in X above and R^5 is selected from hydrogen, C_{1-6} alkyl, $-CH_2F$, phenyl, naphthyl, heterocyclyl or C_{3-7} cycloalkyl; and R^5 is optionally substituted by one or more substituents independently selected from: halo, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, $-CH_2F$, CN, OH, NH_2 , COOH, or $-C(O)OC_{1-6}$ alkyl,
 5 each Z^1 is independently a direct bond, C_{2-6} alkenylene or a group of the formula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$;

R^3 is selected from phenyl or a heterocyclyl, and R^3 is optionally substituted by one or more R^7 groups;

10 R^6 is independently selected from hydrogen, C_{1-6} alkyl or $-C_{2-4}$ alkyl-O- C_{1-4} alkyl;

R^{6a} is independently selected from hydrogen, halo, C_{1-6} alkyl or $-C_{2-4}$ alkyl-O- C_{1-4} alkyl; each R^7 is independently selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_{0-3}$ aryl, $(CH_2)_{0-3}$ heterocyclyl, $(CH_2)_{0-3}C_{3-7}$ cycloalkyl, OH, C_{1-6} alkyl-OH, halo, C_{1-6} alkyl-halo, OC_{1-6} alkyl, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3 , thioxo, NH_2 , CN, $(CH_2)_{0-3}NHSO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}-O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$; $(CH_2)_{0-3}C(O)NHSO_2-R^8$ and $(CH_2)_{0-3}SO_2NHC(O)-R^8$ wherein an alkyl chain, cycloalkyl ring or heterocyclyl
 15 ring within R^7 is optionally substituted by one of more substituents independently selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 , $N-C_{1-4}$ alkylamino, N,N -di- C_{1-4} alkylamino and OC_{1-4} alkyl;

R^8 is selected from hydrogen, C_{1-6} alkyl, aryl, heterocyclyl, C_{3-7} cycloalkyl, OH, C_{1-6} alkyl-OH, COOH, $C(O)OC_{1-6}$ alkyl, $N(R^6)C_{1-6}$ alkyl, OC_{1-6} alkyl,

25 C_{0-6} alkylOC(O) C_{1-6} alkyl, $C(OH)(C_{1-6}$ alkyl) C_{1-6} alkyl; wherein an alkyl chain or aryl, heterocyclyl or cycloalkyl ring within R^8 is optionally substituted by one of more substituents independently selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 , $-NH-C_{1-4}$ alkyl, $-N$ -di- $(C_{1-4}$ alkyl) and OC_{1-4} alkyl;

each a is independently 1, 2 or 3;

30 p is an integer between 0 and 3;

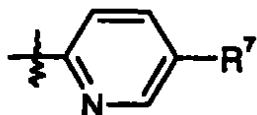
q is an integer between 0 and 3;

and $p + q < 4$.

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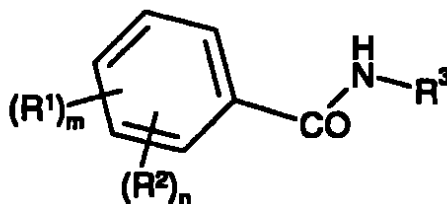
provided that when R^3 is 2-pyridyl and X is other than -Z-, -C(O)-Z-O-Z-,
 -N((R^6)-C(O)-Z-O-Z- or -O-Z-N(R^6)-Z-, then R^3 cannot be mono-substituted at the 5-position
 with an R^7 group selected from COOH or C(O)OC₁₋₆alkyl.

For the avoidance of doubt the numbering in the above proviso is relative to the amide
 5 bond attached to the pyridine ring, thus R^3 in the proviso relates to a group of the following
 structure:



wherein  represents the point of attachment to the amide group in Formula (I).

According to a further feature of the invention there is provided the use of a compound
 10 of Formula (Ia) or a salt thereof, in the preparation of a medicament for use in the treatment or
 prevention of a disease or medical condition mediated through GLK:



Formula (Ia)

wherein

15 m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

and $n + m > 0$;

each R^1 is independently selected from OH, (CH₂)₁₋₄OH, CH₃₋₂F₂, (CH₂)₁₋₄CH₃₋₂F₂,

OCH₃₋₂F₂, halo, C₁₋₆ alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, NH₂, N(C₁₋₆alkyl)C₁₋₆alkyl,

20 CN, phenyl or a heterocyclyl optionally substituted by C₁₋₆alkyl;

each R^2 is the group Y-X-

wherein each X is a linker independently selected from

-O(CH₂)₀₋₃-, -(CH₂)₀₋₃O-, -C(O)O(CH₂)₀₋₃-, -S(CH₂)₀₋₃-, -SO(CH₂)₀₋₃-,

-SO₂(CH₂)₀₋₃-, -NHSO₂-, -SO₂NH-, -N(CH₂)₀₋₃-, -N(CH₂)₁₋₃O(CH₂)₀₋₃-, -(CH₂)₁₋₄-,

25 -CH=CH(CH₂)₀₋₂-, -C≡C(CH₂)₀₋₂-, -NHCO-, -CONH-;

each Y is independently selected from phenyl(CH₂)₀₋₂, naphthyl(CH₂)₀₋₂, heterocyclyl(CH₂)₀₋₂, C₃₋₇ cycloalkyl(CH₂)₀₋₂, C₁₋₆ alkyl, OC₁₋₆alkyl, C₂₋₆ alkenyl, C₂₋₆alkynyl, or CH(OH)CH₃₋₆F_a;

each Y is independently optionally substituted by one or more R⁴ groups;

5 each R⁴ is independently selected from halo, CH₃₋₆F_a, OCH₃₋₆F_a, CN, NH₂, C₁₋₆alkyl, OC₁₋₆alkyl, COOH, (CH₂)₀₋₃COOH, O(CH₂)₀₋₃COOH, C(O)OC₁₋₆alkyl, C₁₋₆alkylC(O)OC₁₋₆alkyl, CO-phenyl, CONH₂, CONH-phenyl, SO₂NH₂, SO₂C₁₋₆alkyl, OH, or phenyl optionally substituted by one or more R⁵ groups, or R^{6b}-X-;

10 R⁵ is selected from hydrogen, C₁₋₆alkyl or C(O)OC₁₋₆alkyl,

R^{6b} is selected from hydrogen, C₁₋₆alkyl, CH₃₋₆F_a phenyl, naphthyl, heterocyclyl or C₃₋₇cycloalkyl; and R^{6b} is optionally substituted by halo, C₁₋₆alkyl, CH₃₋₆F_a, CN, NH₂, COOH and COOC₁₋₆alkyl;

each a is independently 1, 2 or 3;

15 R³ is selected from phenyl or a heterocyclyl, and R³ is optionally substituted by one or more R⁷ groups;

each R⁷ is independently selected from:

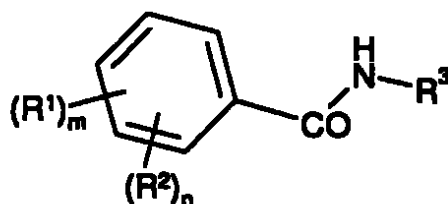
20 C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, heterocyclyl, (CH₂)₀₋₃C₃₋₇cycloalkyl, OH, C₁₋₆alkyl-OH, halo, C₁₋₆alkyl-halo, OC₁₋₆alkyl, SC₁₋₆alkyl, SH, SO₃, NH₂, CN, NHCHO, NSO₂C₁₋₆alkyl, (CH₂)₀₋₃COOH, (CH₂)₀₋₃C(O)OC₁₋₆alkyl, (CH₂)₀₋₃CONH₂, (CH₂)₀₋₃CON(CH₂)₀₋₃R⁸, (CH₂)₀₋₃NH(CH₂)₀₋₃R⁸, (CH₂)₀₋₃NHC(O)(CH₂)₀₋₃R⁸;

R⁸ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, OH, C₁₋₆alkyl-OH, COOH, C(O)OC₁₋₆alkyl, N(C₀₋₆alkyl)C₁₋₆alkyl, O(C₀₋₆alkyl)C₁₋₆alkyl,

25 C₀₋₆alkylOC(O)C₁₋₆alkyl, C(OH)(C₁₋₆alkyl)C₁₋₆alkyl;

provided that when R³ is pyridine, then R⁷ is other than COOH or COOC₁₋₆alkyl.

According to a further feature of the invention there is provided a compound of Formula (Ib) or a salt, solvate or pro-drug thereof;



Formula (Ib)

5 wherein

m is 0, 1 or 2;

n is 1, 2 or 3;

and $n + m$ is 2 or 3;

10 each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_2F$, $-(CH_2)_{1-4}CH_2F$, $-OCH_2F$, halo, OCH_3 , C_2H_5O , $CH_3C(O)O-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN, formyl, phenyl or heterocyclyl optionally substituted by $C_{1-6}alkyl$;

each R^2 is the group $Y-X-$

with the proviso that $Y-X-$ cannot be CH_3O , C_2H_5O or $CH_3C(O)O-$;

15 wherein each X is a linker independently selected from:

$-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$, $-Z-$, $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z-$, $-O-Z-N(R^6)-Z-$, $-O-C(O)-Z-O-Z-$ or a direct

20 bond except where Z is $C_{1-6}alkyl$;

each Z is independently a direct bond, $C_{2-6}alkenylene$ or a group of the formula

$-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$;

each Y is independently selected from aryl- Z^1- , heterocyclyl- Z^1- , $C_{3-7}cycloalkyl-Z^1-$,

$C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-(CH_2)_{1-4}CH_2F$ or $-CH(OH)CH_2F$; wherein

25 each Y is independently optionally substituted by up to 3 R^4 groups;

each R^4 is independently selected from halo, $-CH_2F$, CN, NH_2 , $C_{1-4}alkyl$,

$-OC_{1-6}alkyl$, $-COOH$, $-C(O)OC_{1-6}alkyl$, OH or phenyl optionally substituted by $C_{1-6}alkyl$ or $-C(O)OC_{1-6}alkyl$,

or R^5-X^1 -, where X^1 is independently as defined in X above and R^5 is selected from hydrogen, C_{1-6} alkyl, $-CH_2F$, phenyl, naphthyl, heterocyclyl or C_{3-7} cycloalkyl; and R^5 is optionally substituted by one or more substituents independently selected from: halo, C_{1-6} alkyl, $-OC_{1-6}$ alkyl, $-CH_2F$, CN, OH, NH_2 , COOH, or $-C(O)OC_{1-6}$ alkyl,
 each Z^1 is independently a direct bond, C_{2-6} alkenylene or a group of the formula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q$;

R^3 is heterocyclyl, wherein the atom at the two position of the heterocyclyl ring relative to the amide group, to which R^3 is attached, is a heteroatom and when the atom at the two position of the heterocyclyl ring relative to the amide group is nitrogen, this is an SP^2 hybridised nitrogen, and R^3 is optionally substituted by up to 2 R^7 groups;

R^6 is independently selected from hydrogen, C_{1-6} alkyl or $-C_{2-4}$ alkyl-O- C_{1-4} alkyl;

R^{6a} is independently selected from hydrogen, halo, C_{1-6} alkyl or $-C_{2-4}$ alkyl-O- C_{1-4} alkyl;

each R^7 is independently selected from:

C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_{0-3}$ aryl, $(CH_2)_{0-3}$ heterocyclyl, $(CH_2)_{0-3}C_{3-7}$ cycloalkyl, OH, C_{1-6} alkyl-OH, halo, C_{1-6} alkyl-halo, OC_{1-6} alkyl, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3 , thioxo, NH_2 , CN, $(CH_2)_{0-3}NHSO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)NHSO_2-R^8$ and $(CH_2)_{0-3}SO_2NHC(O)-R^8$ wherein an alkyl chain, cycloalkyl ring or heterocyclyl ring within R^7 is optionally substituted by one of more substituents independently selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 , $N-C_{1-4}$ alkylamino, N,N -di- C_{1-4} alkylamino and OC_{1-4} alkyl;

R^8 is selected from hydrogen, C_{1-6} alkyl, aryl, heterocyclyl, C_{3-7} cycloalkyl, OH, C_{1-6} alkyl-OH, COOH, $C(O)OC_{1-6}$ alkyl, $N(R^6)C_{1-6}$ alkyl, OC_{1-6} alkyl, C_{0-6} alkylOC(O) C_{1-6} alkyl, $C(OH)(C_{1-6}alkyl)C_{1-6}alkyl$; wherein an alkyl chain or aryl, heterocyclyl or cycloalkyl ring within R^8 is optionally substituted by one of more substituents independently selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 , $-NH-C_{1-4}alkyl$, $-N$ -di- $(C_{1-4}alkyl)$ and $OC_{1-4}alkyl$;

each a is independently 1, 2 or 3;

p is an integer between 0 and 3;

q is an integer between 0 and 3;

and $p + q < 4$.

provided that

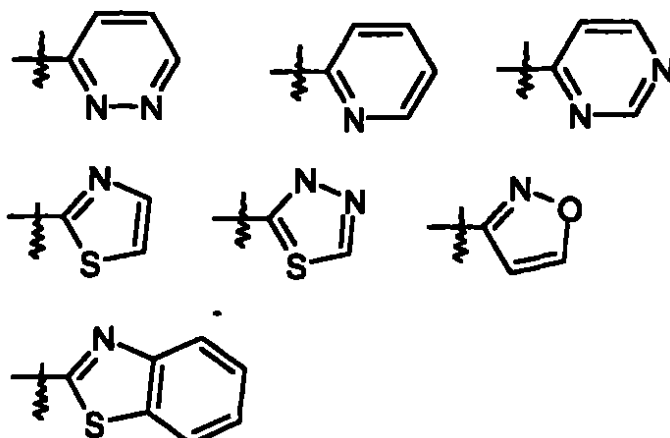
- (i) when R^3 is 2-pyridyl and X is other than -Z-, -C(O)-Z-O-Z-, -N((R^6)-C(O)-Z-O-Z- or
 5 -O-Z-N(R^6)-Z-, then R^3 cannot be mono-substituted at the 5-position with an R^7 group
 selected from COOH or C(O)OC₁₋₆alkyl;
- (ii) positions 3,5 on the phenyl ring (to which R^1 and R^2 are attached) relative to the amide
 bond are substituted and at least one of the groups at position 3 and 5 is an R^2 group;
- (iii) an unbranched, unsubstituted C₁₋₆alkyl chain cannot exceed C₆alkyl in length;
- 10 (iv) when n is 2 or 3 then only one X group can be -NHC(O)-;
- (v) when R^3 is pyridyl and R^7 is halo or methyl then the phenyl ring to which R^2 is attached
 cannot be substituted by an R^2 group at the 2-position relative to the amide bond wherein
 X is -C(O)NH- and Y is optionally substituted phenyl, optionally substituted thienyl or
 optionally substituted pyridyl;
- 15 (vi) when n+m is 2, m is 0 or m is 1 and R^1 is OH, n is 1 and X is -NHC(O)- or n is 2 and X
 is independently selected from -C(O)NH-, -NHC(O)-, -O-, -S(O₂)NH- or a direct bond
 wherein one X group is -NHC(O)-, Y is selected from phenyl, cyclohexyl,
 4,5-dihydro-5-oxo-pyrazolyl, thienyl, 1,3-dihydro-1,3-dioxo-isindolyl,
 2-oxo-1-benzopyran or pyridyl and Y is optionally substituted by R^4 then R^3 cannot be
 20 unsubstituted thiazole, 4,5-dihydro-5-oxo-pyrazolyl substituted by trichlorophenyl,
 4,5,6,7-tetrahydro-benzo[b]thiophene substituted by ethoxycarbonyl or pyridyl optionally
 independently mono or di-substituted by methyl, ethoxy or propylcarbonylamino; and
- (vii) when n+m is 3, m is 0 or 2, R^1 is independently selected from methyl, methoxy or
 hydroxy, n is 1, 2 or 3, X is independently selected from -O-, -S(O₂)NH-, -C(O)-,
 25 -S(O₂)-, -CH₂- or a direct bond, Y is selected from pyrrolidinyl, morpholino, phenyl,
 tetrazolyl or propyl wherein Y is optionally substituted by R^4 and R^4 is selected from
 di-hydroxy, methoxy, C₁₋₄alkyl then R^3 cannot be unsubstituted tetrazolyl, unsubstituted
 thiazolyl or thiazolyl substituted by ethoxycarbonylmethyl.

For the avoidance of doubt C₆alkyl is -CH₂-CH₂-CH₂-CH₂-CH₂-CH₃.

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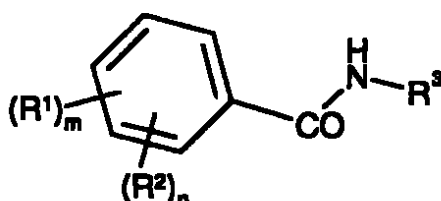
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For the avoidance of doubt examples of R^3 wherein R^3 is heterocyclyl and the atom at the two position of the R^3 heterocyclyl ring, relative to the amide group to which R^3 is attached, is an sp^2 hybridised nitrogen include:



5 wherein  represents the point of attachment to the amide group.

According to a further feature of the invention there is provided a compound of Formula (Ic) or a salt thereof;



Formula (Ic)

10 wherein

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

and $n + m > 0$;

each R^1 is independently selected from OH, $(CH_2)_{1-4}OH$, CH_3-F_n , $(CH_2)_{1-4}CH_3-F_n$,

15 OCH_3-F_n , halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, NH_2 , $N(C_{1-6}alkyl)C_{2-6}alkyl$, CN, phenyl or a heterocyclyl optionally substituted by $C_{1-6}alkyl$;

each R^2 is the group Y-X-

wherein each X is a linker independently selected from

$-O(CH_2)_{0-3}-$, $-(CH_2)_{0-3}O-$, $-C(O)O(CH_2)_{0-3}-$, $-S(CH_2)_{0-3}-$, $-SO(CH_2)_{0-3}-$,

20 $-O_2(CH_2)_{0-3}-$, $-NHSO_2-$, $-SO_2NH-$, $-N(CH_2)_{0-3}-$, $-N(CH_2)_{1-3}O(CH_2)_{0-3}-$, $-(CH_2)_{1-4}-$,

$-CH=CH(CH_2)_{0-2}-$, $-C\equiv C(CH_2)_{0-2}-$, $-NHCO-$, $-CONH-$;

each Y is independently selected from phenyl(CH₂)₀₋₂, naphthyl(CH₂)₀₋₂, heterocyclyl(CH₂)₀₋₂, C₃₋₇ cycloalkyl(CH₂)₀₋₂, C₂₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, or CH(OH)CH₃₋₈F_n;

each Y is independently optionally substituted by one or more R⁴ groups;

5 each R⁴ is independently selected from halo, CH₃₋₈F_n, OCH₃₋₈F_n, CN, NH₂, C₁₋₆alkyl, OC₁₋₆alkyl, COOH, (CH₂)₀₋₃COOH, O(CH₂)₀₋₃COOH, C(O)OC₁₋₆alkyl, C₁₋₆alkylC(O)OC₁₋₆alkyl, CO-phenyl, CONH₂, CONH-phenyl, SO₂NH₂, SO₂C₁₋₆alkyl, OH, or phenyl optionally substituted by one or more R⁵ groups, or R^{6b}-X-;

10 R⁵ is selected from hydrogen, C₁₋₆alkyl or C(O)OC₁₋₆alkyl, R^{6b} is selected from hydrogen, C₁₋₆alkyl, CH₃₋₈F_n, phenyl, naphthyl, heterocyclyl or C₃₋₇cycloalkyl; and R^{6b} is optionally substituted by halo, C₁₋₆alkyl, CH₃₋₈F_n, CN, NH₂, COOH and COOC₁₋₆alkyl;

each a is independently 1, 2 or 3;

15 R³ is a heterocyclyl, and R³ is optionally substituted by one or more R⁷ groups; each R⁷ is independently selected from:

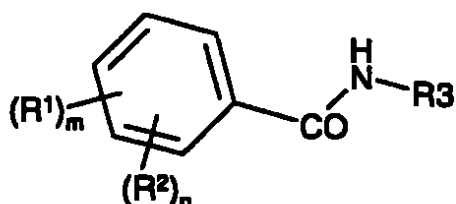
20 C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, heterocyclyl, (CH₂)₀₋₃C₃₋₇cycloalkyl, OH, C₁₋₆alkyl-OH, halo, C₁₋₆alkyl-halo, OC₁₋₆alkyl, SC₁₋₆alkyl, SH, SO₃, NH₂, CN, NHCHO, NSO₂C₁₋₆alkyl, (CH₂)₀₋₃COOH, (CH₂)₀₋₃C(O)OC₁₋₆alkyl, (CH₂)₀₋₃CONH₂, (CH₂)₀₋₃CON(CH₂)₀₋₃R⁸, (CH₂)₀₋₃NH(CH₂)₀₋₃R⁸, (CH₂)₀₋₃NHC(O)(CH₂)₀₋₃R⁸;

R⁸ is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, OH, C₁₋₆alkyl-OH, COOH, C(O)OC₁₋₆alkyl, N(C₀₋₆ alkyl)C₁₋₆ alkyl, O(C₀₋₆ alkyl)C₁₋₆ alkyl, C₀₋₆alkylOC(O)C₁₋₆alkyl, C(OH)(C₁₋₆alkyl)C₁₋₆alkyl;

25 provided that

- (i) when R³ is thiazole and R⁷ is nitro, then at least one R² group is other than -O-propene;
- (ii) when R³ is pyrimidine or pyridine, then R¹ is other than OH;
- (iii) when R³ is pyridine, then R⁷ is other than COOH or COOC₁₋₆alkyl.

30 A further feature of the invention is a compound of Formula (Id) or a salt, solvate of pro-drug thereof;



Formula (Id)

wherein

R^3 is phenyl, optionally substituted by one or more R^7 groups;

- 5 $m, n, \text{R}^1, \text{R}^2, \text{X}, \text{Y}, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8$, and a are as defined above for a Compound of Formula (I).

Compounds of Formula (I), (Ia), (Ib), (Ic), or (Id) 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.

- 10 When m is 2, each R^1 group may be the same or different; preferably both R^1 groups are the same. When n is 2, 3 or 4, each R^2 group may be the same or different to any other R^2 group; preferably at least two R^2 groups are different. The R^1 and/or R^2 group(s) may be attached at the -2, -3, -4, -5 or -6 positions.

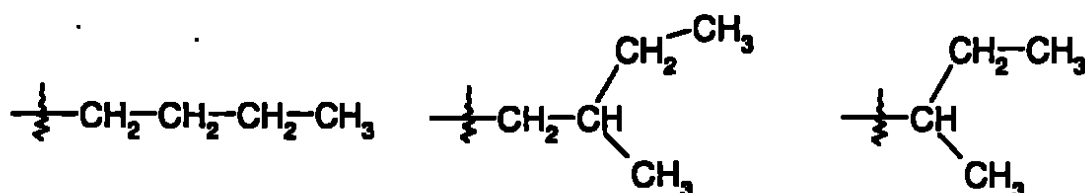
- The term "aryl" refers to phenyl, naphthyl or a partially saturated bicyclic carbocyclic ring containing between 8 and 12 carbon atoms, preferably between 8 and 10 carbon atoms. Example of partially saturated bicyclic carbocyclic ring include: 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl, 1,2,4a,5,8,8a-hexahydronaphthyl or 1,3a-dihydropentalene.

- 20 The term "halo" includes chloro, bromo, fluoro and iodo; preferably chloro, bromo and fluoro; most preferably fluoro.

- The expression " $-\text{CH}_{3-a}\text{F}_a$ " wherein a is an integer between 1 and 3 refers to a methyl group in which 1, 2 or all 3 hydrogen are replaced by a fluorine atom. Examples include: trifluoromethyl, difluoromethyl and fluoromethyl. An analogous notation is used with reference to the group $-(\text{CH}_2)_{1-4}\text{CH}_{3-a}\text{F}_a$, examples include: 2,2-difluoroethyl and 3,3,3-trifluoropropyl.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups. For example, " C_{1-4} alkyl" includes propyl, isopropyl and *t*-butyl. For the avoidance of doubt, an alkyl chain can be joined to the rest of the molecule at the end of the alkyl

chain or in the middle of an alkyl chain, i.e. the definition of "alkyl" includes the following structures:



wherein  represents the point of attachment to the rest of the molecule.

- 5 A "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or fused bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, wherein a -CH₂- group can optionally be replaced by a -C(O)- or sulphur atoms in a heterocyclic ring may be oxidised to S(O) or S(O)₂. A 'heterocyclyl ring may, unless otherwise specified, be carbon or nitrogen linked, unless linking via nitrogen leads to a
- 10 charged quaternary nitrogen.

Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic or fused bicyclic ring wherein each ring contains 5 or 6 atoms of which 1 to 3 atoms are nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or sulphur atoms in a

15 heterocyclic ring may be oxidised to S(O) or S(O)₂ groups.

Examples and suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouracilyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-

20 azabicyclo[2.2.1]heptyl, 4-thiazolidonyl, morpholino, 2-oxotetrahydrofuranyl, tetrahydrofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, isoxazolyl, tetrahydropyranyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiazolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,2,3-

25 triazolyl, pyranlyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl.

Preferably the term "heterocyclyl" refers to monocyclic heterocyclic rings with 5- or 6-membered systems, such as isoxazolyl, pyrrolidinyl, 2-pyrrolidonyl, 2,5-dioxopyrrolidinyl, morpholino, tetrahydrofuranyl, piperidyl, piperazinyl, thiomorpholino, tetrahydropyranyl,

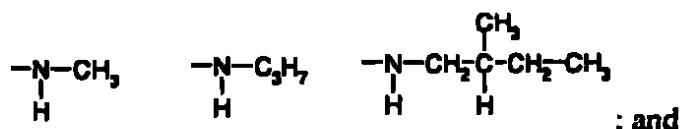
thienyl, imidazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, indolyl, thiazolyl, thiadiazolyl, pyrazinyl, pyridazinyl and pyridyl.

Preferred examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, 5 benzisoxazolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinoliny, isoquinoliny, quinoxaliny, quinazoliny, phthalazinyl, cinnoliny and naphthyridiny.

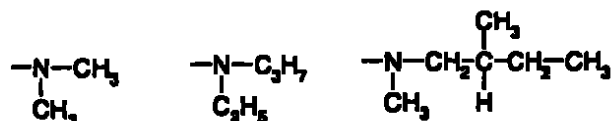
The term "cycloalkyl" refers to a saturated carbocyclic ring containing between 3 to 12 carbon atoms, preferably between 3 and 7 carbon atoms. Examples of C₃₋₇cycloalkyl include cycloheptyl, cyclohexyl, cyclopentyl, cyclobutyl or cyclopropyl. Preferably cyclopropyl,

10 cyclopentyl or cyclohexyl.

Examples of C₁₋₄alkyl include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl and 2-ethyl-butyl; examples of C₁₋₄alkyl-OH include hydroxymethylen and hydroxyethylene; examples of C₁₋₄alkyl-halo include chloromethylene, fluoromethylene, chloroethylene and fluoroethylene; examples of C₂₋₄alkenyl include: ethenyl, 2-propenyl, 2-butenyl, or 15 2-methyl-2-butenyl; examples of C₂₋₄alkynyl include: ethynyl, 2-propynyl, 2-butylnyl, or 2-methyl-2-butylnyl, examples of -OC₁₋₄alkyl include methoxy, ethoxy, propoxy and *tert*-butoxy; examples of -C(O)OC₁₋₄alkyl include methoxycarbonyl, ethoxycarbonyl and *tert*-butyloxycarbonyl; examples of -NH-C₁₋₄alkyl include:



20 examples of -N-di-(C₁₋₄alkyl):



For the avoidance of doubt, in the definition of linker group 'X', the right hand side of the group is attached to the phenyl ring and the left hand side is bound to 'Y'. The same orientation applies to the linker group 'X¹', thus the right hand side of 'X¹' is attached to Y 25 and the left hand side is attached to 'R⁵'.

It is to be understood that, insofar as certain of the compounds of Formula (I), (Ia), (Ib), (Ic) and (Id) defined above or compounds of Formula (II) to (IIIk) defined below 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

5 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.

Preferred compounds of Formula (I), (Ia), (Ib), (Ic), and (Id) above, and of compounds of Formula (II) to (IIIk) below are those wherein any one or more of the following apply:

- 10 (1) m is 0 or 1;
n is 1 or 2; preferably n is 2;
most preferably m is 0 and n is 2.
- (2) The R^1 and/or R^2 group(s) are attached at the 2-position and/or the 3-position and/or the 5- position; when $n + m$ is 3, the groups are preferably at the 2-, 3- and 5-
15 positions; when $n + m$ is 2, the groups are preferably at the 2- and 5- or the 3- and 5- positions; most preferably there are two groups in total, substituted at the 3- and 5- positions.
- (3) each R^1 is independently selected from OH, formyl, CH_3-F_n (preferably CF_3), OCH_3-F_n , halo, C_{1-6} alkyl, NH_2 , CN, $(CH_2)_{1-4}OH$ or a heterocyclyl optionally substituted by
20 C_{1-6} alkyl;
Preferably R^1 is selected from:
OH, formyl, CH_3-F_n (preferably CF_3), OCH_3-F_n (preferably OCF_3), halo, C_{1-4} alkyl (preferably methyl), NH_2 , CN and $(CH_2)_{1-4}OH$;
Most preferably R^1 is selected from:
25 OH, formyl, NH_2 , halo (preferably chloro) or $(CH_2)_{1-4}OH$.
- (4) each R^2 is the group Y-X-
wherein each X is independently selected from:
-Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -OC(O)-Z-, -C(O)-Z-O-Z-,
-O-C(O)-Z-O-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R⁶)-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z-,
30 -N(R⁶)-C(O)-Z-O-Z-, -SO₂N(R⁶)-Z-, -N(R⁶)SO₂-Z- or -O-Z-N(R⁶)-Z-;
preferably each X is selected from:

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-Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -C(O)-Z-O-Z-, -O-C(O)-Z-O-Z-,
-N(R⁶)-Z-, -N(R⁶)CO-Z-, -N(R⁶)-C(O)-Z-O-Z- or -O-Z-N(R⁶)-Z-;

further preferably each X is selected from:

-Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -C(O)-Z-O-Z-, -N(R⁶)-Z-, or
-N(R⁶)CO-Z-;

Most preferably each X is selected from:

-CH=CH-Z-, -O-Z- or -C(O)-Z-.

each Z is independently selected from:

a direct bond, -(CH₂)₁₋₂, or a group of the formula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q-,

wherein R^{6a} is independently selected from hydrogen and C₁₋₄alkyl;

preferably a direct bond, -(CH₂)₁₋₂- or a group of the formula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q-,

wherein R^{6a} is independently selected from hydrogen and C₁₋₄alkyl and p and q are
independently 0 or 1;

more preferably a direct bond, -CH₂- or -C(CH₃)₂-.

and each Y is independently selected from:

C₁₋₆alkyl, C₂₋₆alkenyl, aryl-Z¹-, heterocyclyl-Z¹-, C₃₋₇ cycloalkyl(CH₂)₀₋₂,
-(CH₂)₁₋₄CH₃₋₄F₁;

preferably each Y is selected from:

C₁₋₆alkyl (preferably a branched chain C₂₋₆ alkyl such as isopropyl, isobutyl, etc) ,
C₂₋₆alkenyl, phenyl-Z¹- or heterocyclyl-Z¹-,

Most preferably each Y is selected from:

-CH₃ -, -C₂H₅-, prop-2-yl, iso-propyl, 1-methyl-propyl, 2-methyl-propyl, allyl, phenyl,
2-ethyl-butyl, phenyl-Z¹-, cyclopropyl-Z¹-, cyclopentyl-Z¹-, morpholino-Z¹-,
piperidinyl-Z¹-, piperazinyl-Z¹-, pyrrolidinyl-Z¹-, tetrahydro-2H-pyranyl-Z¹-,
isoxazolyl-Z¹-, oxazolyl-Z¹-, pyridyl-Z¹-, thiazolyl-Z¹-, thienyl-Z¹- or
isoindoliny-Z¹-,

each Z¹ is independently selected from:

a direct bond, -(CH₂)₁₋₂, or a group of the formula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q-,

wherein R^{6a} is independently selected from hydrogen and C₁₋₄alkyl;

preferably a direct bond, -(CH₂)₁₋₂- or a group of the formula

-(CH₂)_p-C(R^{6a})₂-(CH₂)_q-, wherein R^{6a} is independently selected from hydrogen
and C₁₋₂alkyl and p and q are independently 0 or 1;

further preferably a direct bond, $-\text{CH}_2-$, $-\text{CH}_2\text{-CH}(\text{CH}_3)-$ or $-(\text{CH}_2)_2-$;

most preferably a direct bond, $-\text{CH}_2-$ or $-(\text{CH}_2)_2-$

wherein in each of the above Y is independently optionally substituted by R^4 .

(5) each R^2 is the group Y-X- , Z within the definition of X is a direct bond and Z^1 within the
5 definition of Y is a group of the formula $-(\text{CH}_2)_p\text{-C}(\text{R}^{6a})_2\text{-(CH}_2)_q-$.

(6) each R^4 is independently selected from

halo, $\text{CH}_3\text{-F}$ (ideally CF_3), $\text{OCH}_3\text{-F}$ (ideally OCF_3), CN, $\text{C}_{1-6}\text{alkyl}$, $\text{OC}_{1-6}\text{alkyl}$,
COOH, $\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$, $(\text{CH}_2)_{0-3}\text{COOH}$, $\text{O}(\text{CH}_2)_{0-3}\text{COOH}$, CO-phenyl, CONH_2 ,
CONH-phenyl, SO_2NH_2 , $\text{SO}_2\text{C}_{1-6}\text{alkyl}$, OH, or phenyl optionally substituted by one
10 or more R^5 groups where R^5 is selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$ or
 $\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$;

Preferably each R^4 is selected from

halo, CN, $\text{C}_{1-6}\text{alkyl}$, $\text{OC}_{1-6}\text{alkyl}$ or COOH.

(7) each R^5 is selected from:

15 $\text{C}_{1-6}\text{alkyl}$, phenyl, heterocyclyl or $\text{C}_{3-7}\text{cycloalkyl}$;

Preferably each R^5 is selected from:

$\text{C}_{1-6}\text{alkyl}$, tetrahydrofuranyl, imidazolyl, isoxazolyl, pyrazinyl, pyrimidinyl, thienyl,
1,3-benzodioxole, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

Most preferably each R^5 is selected from:

20 CH_3 , C_2H_5 , prop-2-yl, tetrahydrofuranyl, imidazolyl, isoxazolyl, pyrazinyl,
pyrimidinyl, thienyl, 1,3-benzodioxolyl or cyclopentyl;

(8) each X^1 is independently selected from:

a direct bond, $-\text{Z-}$, $-\text{O-C}(\text{O})\text{-Z-}$, $-\text{C}(\text{O})\text{-O-Z-}$, $-\text{C}(\text{O})\text{-Z-}$, $-\text{N}(\text{R}^6)\text{-C}(\text{O})\text{-Z-}$,
 $-\text{C}(\text{O})\text{-N}(\text{R}^6)\text{-Z-}$, $-\text{S}(\text{O}_2)\text{-Z-}$, $-\text{N}(\text{R}^6)\text{SO}_2\text{-Z-}$ or $-\text{SO}_2\text{N}(\text{R}^6)\text{-Z-}$;

25 Preferably each X^1 is independently selected from:

a direct bond, $-\text{Z-}$, $-\text{O-C}(\text{O})\text{-Z-}$, $-\text{C}(\text{O})\text{-Z-}$, $\text{N}(\text{R}^6)\text{-C}(\text{O})\text{-Z-}$ or $-\text{S}(\text{O}_2)\text{-Z-}$;

Most preferably each X^1 is independently selected from:

a direct bond, $-\text{CH}_2-$, $-\text{O-C}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{CH}_3)\text{-C}(\text{O})\text{-CH}_2-$ or $-\text{S}(\text{O})_2-$;

(9) optional substituents on R^5 are independently selected from:

30 OH, CN, NH_2 , $\text{C}_{1-6}\text{alkyl}$, $\text{OC}_{1-6}\text{alkyl}$ or halo;

Preferably optional substituents on R^5 are independently selected from:

OH, $\text{C}_{1-6}\text{alkyl}$, $\text{OC}_{1-6}\text{alkyl}$ or halo;

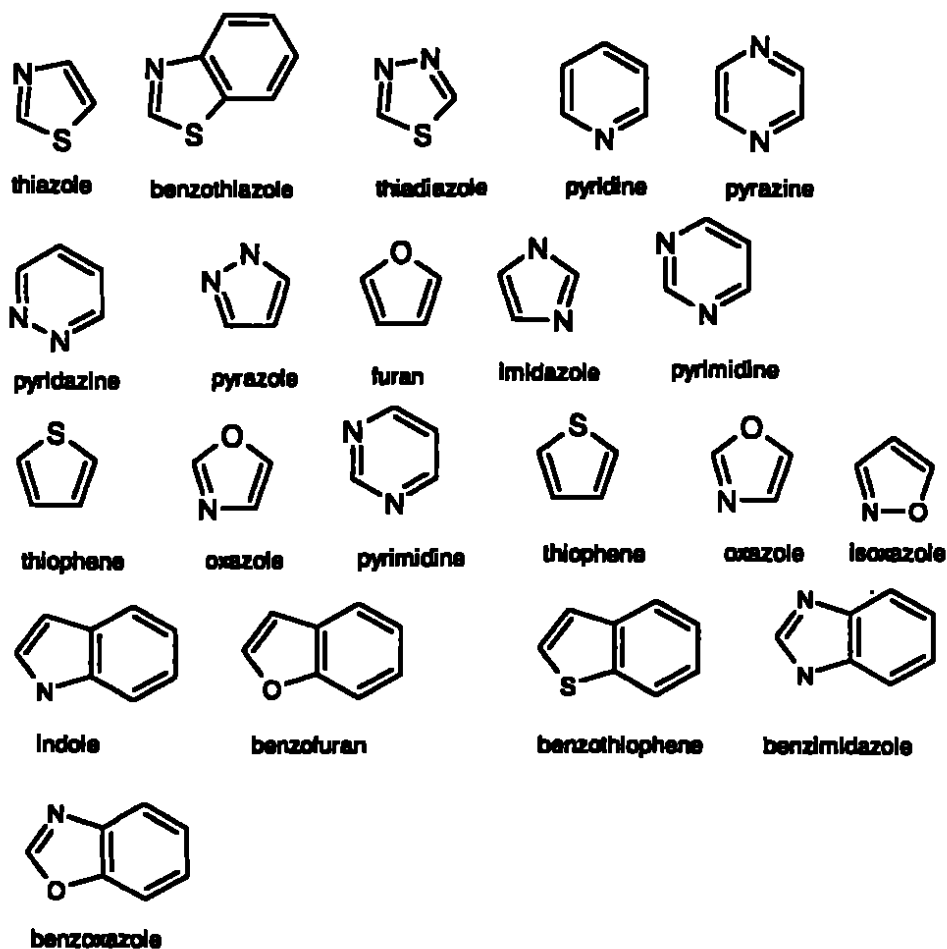
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Most preferably optional substituents on R^3 are independently selected from:

OH, CH₃, t-butyl, OCH₃, chloro or fluoro;

(10) R^3 is a heterocyclyl (preferably a nitrogen-containing heterocyclyl group), optionally substituted by one or more R^7 groups;

5 Preferably R^3 is a heterocyclyl selected from the following:



More preferably R^3 is selected from:

thiazole, thiadiazole, pyridine, pyrazine, pyridazine, pyrazole, pyrimidine, isoxazole, furan, benzothiazole, benzimidazole and benzoxazole.

10 Further preferably R^3 is selected from:

thiazole, benzothiazole, thiadiazole, pyridine, pyrazine, pyridazine, pyrazole, imidazole, pyrimidine, oxazole and indole.

Most preferably R^3 is selected from:

pyridine, thiazole or thiadiazole.

15 In a further embodiment of the invention, R^3 is selected from:

benzothiazole, thiazole, thiadiazole, pyridine, pyrazine, pyridazine, pyrazole, pyrimidine, isoxazole and furan.

(11) R^3 is not substituted or is substituted by one R^7 group.

(12) each R^7 is independently selected from:

5 OH, CN, NH_2 , SO_3 , thioxo, halo, C_{1-6} alkyl, C_{1-6} alkyl-OH, O- C_{1-6} alkyl, C_{1-6} alkyl-halo, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $-(CH_2)_{0-3}S(O)_{0-2}R^8$, $-(CH_2)_{0-3}N(R^6)SO_2R^8$, $(CH_2)_{0-3}C(O)N(R^6)S(O)_2R^8$ or $(CH_2)_{0-3}$ heterocyclyl;

preferably R^7 is selected from:

10 OH, CN, NH_2 , SO_3 , thioxo, halo, C_{1-4} alkyl, C_{1-4} alkyl-OH, O- C_{1-4} alkyl, C_{1-4} alkyl-halo, $(CH_2)_{0-1}COOH$, $(CH_2)_{0-1}C(O)OR^8$, $(CH_2)_{0-1}NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}NHC(O)(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$, $-(CH_2)_{0-2}S(O)_{0-2}R^8$, $-(CH_2)_{0-1}N(R^6)SO_2R^8$, $(CH_2)_{0-1}C(O)N(R^6)S(O)_2R^8$ or $(CH_2)_{0-1}$ heterocyclyl (preferably the heterocyclyl is selected from furanyl, morpholino, 5-oxo-oxadiazolyl or tetrazolyl);

further preferably R^7 is selected from:

$COOH$, $C(O)OC_{1-6}$ alkyl, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-3}C(O)NHSO_2R^8$ or $(CH_2)_{0-3}SO_2NHC(O)-R^8$;

most preferably R^7 is selected from:

20 $COOH$, $C(O)OC_{1-6}$ alkyl or $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$,

(13) R^8 is selected from:

hydrogen, OH, $COOH$, C_{1-6} alkyl, O- C_{1-6} alkyl, $-C(O)-O-C_{1-6}$ alkyl, C_{0-6} alkylOC(O) C_{1-6} alkyl, $N(R^6)C_{1-6}$ alkyl, aryl, heterocyclyl or C_{3-7} cycloalkyl;

Preferably R^8 is selected from:

25 hydrogen, OH, $COOH$, CH_3 , isopropyl, 2-methyl-butyl, pent-3-yl, $-O-CH_3$, $-C(O)-O-C_2H_5$, $-CH_2-O-C(O)-CH_3$, $-CH_2-O-C(O)-C_2H_5$, $-C(CH_3)_2-O-C(O)-CH_3$, NH-isopropyl, NH-t-butyl, $N(CH_3)-CH_3$, phenyl, isoxazolyl, pyrazolyl, pyridyl, thienyl, cyclopropyl or cyclobutyl;

(14) Preferred optional substituents on R^8 are independently selected from:

30 OH, CN, NH_2 , halo or C_{1-6} alkyl;

More preferred optional substituents on R^8 are independently selected from:

OH, halo or C_{1-6} alkyl;

More preferred optional substituents on R^8 are independently selected from:

OH, chloro, fluoro and CH_3 .

For example, particularly preferred compounds of the invention are those wherein:

m is 0 and n is 2, the two R^2 groups are attached at the 2- and 5- or the 3- and 5- positions (ideally the 3- and 5- positions), and X is $-O(CH_2)_{0-2}-$ (ideally $-OCH_2-$); or

m is 0 and n is 2, the two R^2 groups are attached at the 2- and 5- or the 3- and 5- positions (ideally the 3- and 5- positions), X is $-O(CH_2)_{0-2}-$ (ideally $-O-$ or $-OCH_2-$), and Y is benzyl optionally substituted by halo (such as fluoro or chloro, ideally fluoro) or C_{1-6} alkyl; or

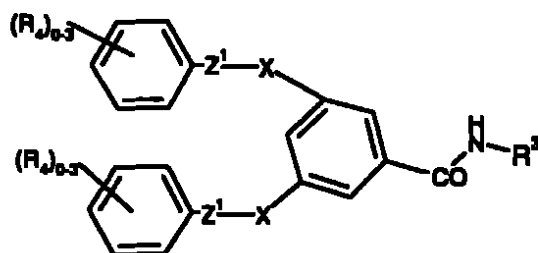
m is 0 and n is 2, the two R^2 groups are attached at the 2- and 5- or the 3- and 5- positions (ideally the 3- and 5- positions), X is $-O(CH_2)_{0-2}-$ (ideally $-O-$ or $-OCH_2-$), and R^3 is a heterocyclyl optionally substituted by R^7 ; or

m is 0 and n is 2, the two R^2 groups are attached at the 2- and 5- or the 3- and 5- positions (ideally the 3- and 5- positions), X is $-O-$ or $-O(CH_2)_{0-2}-$ (ideally $-O-$ or $-OCH_2-$), Y is phenyl optionally substituted by halo (such as fluoro or chloro, ideally fluoro) or C_{1-6} alkyl, and R^3 is a heterocyclyl optionally substituted by R^7 ; or

m is 1 and n is 1, the R^1 and R^2 groups are attached at the 2- and 5- or the 3- and 5- positions (ideally the 3- and 5- positions), R^1 is halo (such as fluoro, chloro), and X is $-O(CH_2)_{0-2}-$ (ideally $-O-$ or $-OCH_2-$).

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

(I) a compound of Formula (II)



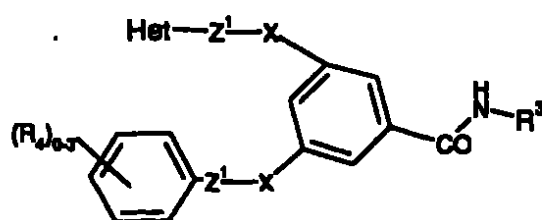
Formula (II)

wherein:

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(II) a compound of Formula (IIa)

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Formula (IIa)

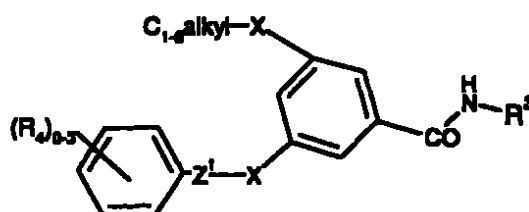
wherein:

Het is a monocyclic heterocyclyl, optionally substituted with up to 3 groups selected from R^4 and,

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

(III) a compound of Formula (IIb)



Formula (IIb)

wherein:

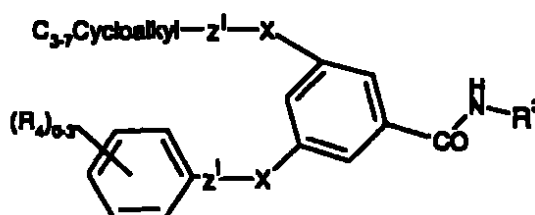
the $\text{C}_{1-6}\text{alkyl}$ group is optionally substituted with up to 3 groups selected from R^4 , preferably unsubstituted;

the $\text{C}_{1-6}\text{alkyl}$ group optionally contains a double bond, preferably the $\text{C}_{1-6}\text{alkyl}$ group does not contain a double bond; and

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

(IV) a compound of Formula (IIc)



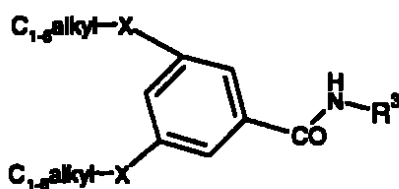
Formula (IIc)

wherein:

the $\text{C}_{3-7}\text{cycloalkyl}$ group is optionally substituted with up to 3 groups selected from R^4 , and

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(V) a compound of Formula (IIId)



Formula (IIId)

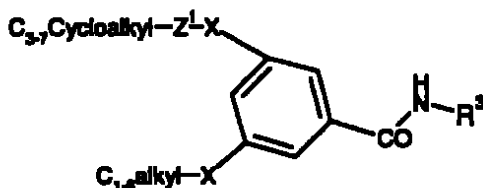
wherein:

the C_{1-6} alkyl groups are independently optionally substituted with up to 3 groups selected from R^4 , preferably one of the C_{1-6} alkyl groups is unsubstituted,

the C_{1-6} alkyl groups independently optionally contain a double bond, preferably only one of the C_{1-6} alkyl groups contain a double bond, preferably neither of the C_{1-6} alkyl group contains a double bond, and

X , R^3 and R^4 are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(VI) a compound of Formula (IIe)



Formula (IIe)

wherein:

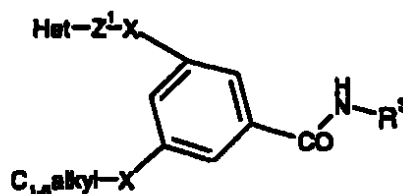
the C_{3-7} cycloalkyl and C_{1-6} alkyl groups are independently optionally substituted with up to 3 groups selected from R^4 , preferably the C_{1-6} alkyl group is unsubstituted;

the C_{1-6} alkyl group optionally contains a double bond, preferably the C_{1-6} alkyl group does not contains a double bond; and

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(VII) a compound of Formula (IIf)

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Formula (IIe)

wherein:

Het is a monocyclic heterocyclyl,

5 the Het and $\text{C}_{1-6}\text{alkyl}$ groups are independently optionally substituted with up to 3 groups selected from R^4 , preferably the $\text{C}_{1-6}\text{alkyl}$ group is unsubstituted;

the $\text{C}_{1-6}\text{alkyl}$ group optionally contains a double bond, preferably the $\text{C}_{1-6}\text{alkyl}$ group does not contains a double bond; and

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);

10 or a salt, solvate or pro-drug thereof.

A further preferred group of compounds of group (VII) comprise compounds of Formula (IIf) wherein:

Het is a saturated monocyclic heterocyclyl;

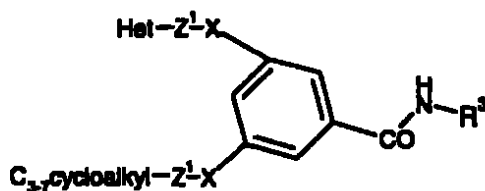
X is $-\text{Z}-$, preferably $-\text{CH}_2-$;

15 R^4 is a group of $\text{R}^5\text{-X}^1$;

X^1 is as defined for a compound of Formula (I);

R^5 is $\text{C}_{1-6}\text{alkyl}$, phenyl, heterocyclyl, each of which is optionally substituted as defined for a compound of Formula (I);

(VIII) a compound of Formula (IIg)



Formula (IIg)

wherein:

Het is a monocyclic heterocyclyl,

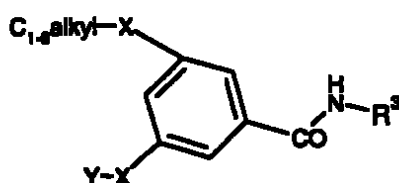
the Het and $\text{C}_{3-7}\text{cycloalkyl}$ groups are independently optionally substituted with up

25 to 3 groups selected from R^4 , and

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

(IX) a compound of Formula (IIh)

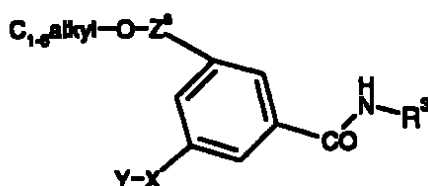


Formula (IIh)

wherein:

- 5 Y is aryl-Z¹-, wherein aryl is preferably a partially saturated bicyclic carbocyclic ring;
 Y and the C₁₋₆alkyl group are independently optionally substituted with up to 3 groups
 selected from R⁴, preferably the C₁₋₆alkyl group is unsubstituted,
 the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does
 not contains a double bond; and
 10 X, Z¹, R³ and R⁴ are as defined above in a compound of Formula (I);
 or a salt, solvate or pro-drug thereof.

(X) a compound of Formula (IIj)



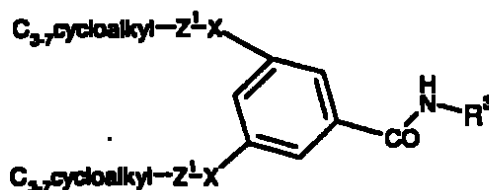
Formula (IIj)

15 wherein:

- X is selected from -SO₂N(R⁶)-Z- or -N(R⁶)SO₂-Z-, preferably X is -SO₂N(R⁶)-Z-;
 Z is as described above, preferably Z is propylene, ethylene or methylene, more
 preferably Z is methylene;
 Z² is selected from a direct bond or a group of the formula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q-;
 20 preferably Z² is selected from C₁₋₂alkylene or a direct bond; preferably Z² is a direct
 bond;
 R^{6a} is selected from: C₁₋₄alkyl or hydrogen, preferably methyl or hydrogen;
 Y is selected from aryl-Z¹- or heterocyclyl-Z¹-;
 Y and the C₁₋₆alkyl group are independently optionally substituted with up to 3 groups
 25 selected from R⁴,
 the C₁₋₆alkyl group optionally contains a double bond, preferably the C₁₋₆alkyl group does
 not contain a double bond, and

Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);
or a salt, solvate or pro-drug thereof.

(XI) a compound of Formula (III)



Formula (III)

wherein:

the C_{3-7} cycloalkyl groups are independently optionally substituted with up to 3 groups selected from R^4 , and

X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I);

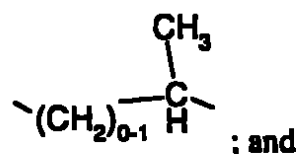
or a salt, solvate or pro-drug thereof.

A further preferred groups of compounds of the invention in either of groups (I)-(XI) above is wherein:

X is independently selected from: $-O-Z-$, $SO_2N(R^6)-Z-$ or $-N(R^6)-Z-$;

Z is a direct bond or $-CH_2-$;

Z^1 is selected from a direct bond, $-CH_2-$, $-(CH_2)_2-$ or



R^3 is as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

A further preferred groups of compounds of the invention in either of groups (I)-(XI)

above is wherein:

R^3 is substituted by at least one R^7 group (preferably one R^7 group);

R^7 is a group of the formula $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}N(R^6)S(O)_2R^8$ or

$(CH_2)_{0-3}$ heterocyclyl (preferably 5-oxo-1,2,4-oxadiazol-3-yl or -tetrazol-5-yl);

R^3 , R^6 and R^8 are as defined above in a compound of Formula (I);

or a salt, solvate or pro-drug thereof.

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);
- 5 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
- 10 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

15 C₁ to C₆alkoxymethyl esters for example methoxymethyl, C₁ to C₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃ to C₆cycloalkoxycarbonyloxy C₁ to C₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁-C₆alkoxycarbonyloxyethyl esters.

20 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.

25 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

30 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.

A further feature of the invention is a pharmaceutical composition comprising a compound of Formula (I) to (Id) or (II) to (IIIk) as defined above, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable diluent or carrier.

10 According to another aspect of the invention there is provided a compound of Formula (Ib) to (Id), or (II) to (IIIk) as defined above for use as a medicament; provided that when R^3 is 2-pyridyl and X is other than -Z-, -C(O)-Z-O-Z-, -N((R^6)-C(O)-Z-O-Z- or -O-Z-N(R^6)-Z-, then R^3 cannot be mono-substituted at the 4-position with an R^7 group selected from COOH or C(O)OC₁₋₆alkyl.

15 Further according to the invention there is provided a compound of Formula (Ib) to (Id), or (II) to (IIIk) for use 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.

20 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 (Ib) to (Id), or (II) to (IIIk), or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

Specific disease which may be treated by the compound or composition of the invention include: blood glucose lowering in Diabetes Mellitus type 2 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 "Diabetes" 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 (Ib) to (Id), or (II) to (IIIk), or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the combined treatment or prevention of diabetes and obesity.

According to another aspect of the invention there is provided the use of a compound of Formula (Ib) to (Id), or (II) to (IIIk), or salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the treatment or prevention 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 (Ib) to (Id), or (II) to (IIIk), or salt, solvate or pro-drug 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 (Ib) to (Id), or (II) to (IIIk), or salt, solvate or pro-drug thereof, to a mammal in need of such treatment.

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

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

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

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

- 5 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 polyoxyethylene stearate), or
- 10 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
- 15 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
- 20 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
- 25 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
- 30 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 may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. 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) and prandial glucose regulators (for example repaglinide, nateglinide);
- 3) Insulin sensitising agents including PPAR γ agonists (for example pioglitazone and rosiglitazone);
- 4) Agents that suppress hepatic glucose output (for example metformin).
- 5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
- 6) Agents designed to treat the complications of prolonged hyperglycaemia;
- 7) Anti-obesity agents (for example sibutramine and orlistat);
- 8) Anti-dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α 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);

- 9) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg
5 lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg
candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
- 10) 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
10 molecular weight analogues, hirudin) and warfarin; and
- 11) 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, solvates and
15 pro-drugs thereof.

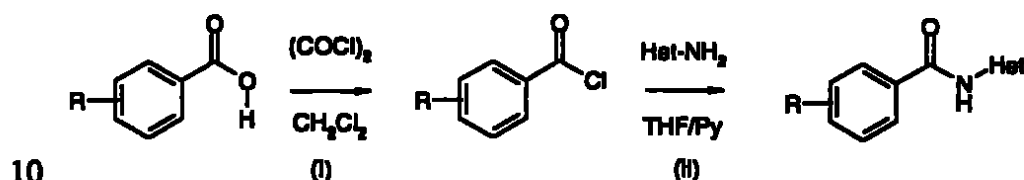
A compound of the invention, or a salt thereof, may be prepared by any process known
to be applicable to the preparation of such compounds or structurally related compounds.
Such processes are illustrated by the following representative schemes (Routes 1 - 18) in
which variable groups have any of the meanings defined for formula (I) unless stated
20 otherwise. 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.

25 The condensation of an acid with a heterocyclic amine (Route 1) is used in the
preparation of compounds of the invention or in the preparation of intermediates to the final
products. One or more further reactions (such as ester hydrolysis, Routes 2a and 2b) may then
be performed on these intermediates. The amide-forming reaction (Route 1) is best
accomplished via the acid chloride, which is usually prepared using oxalyl chloride. However,
30 alternative methods for acid chloride formation (such as resin-bound triphenyl phosphine with
carbon tetrachloride and dichloromethane) may also be employed. Additionally, alternative

methods of amide-bond formation (such as a peptide coupling agent such as EDC or HATU, with or without additives such as DIPEA or DMAP) may be used.

The remaining preparative routes (Routes 2 - 18) consist of further manipulation of the compound with the amide bond in place. Further preparative routes are summarise in Routes 5 19 - 29. Examples of routes 1-29 are provided in the examples below. Reagents and conditions given are only for illustration and alternative methods may generally be employed.

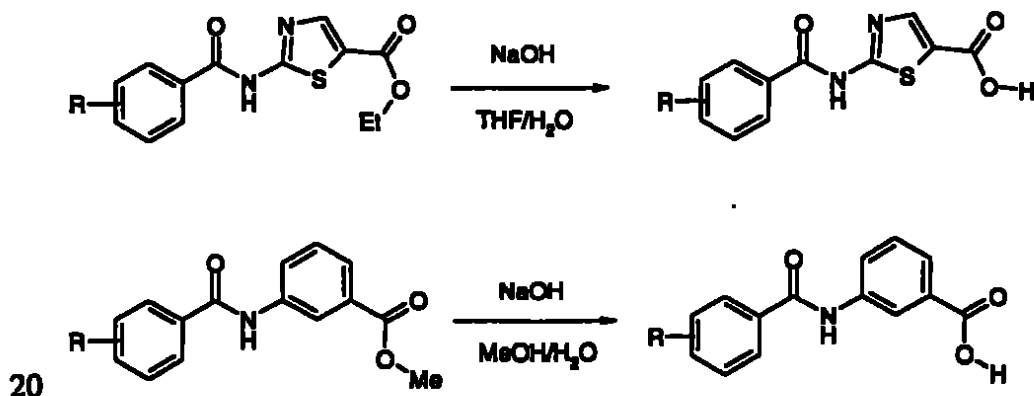
Route 1



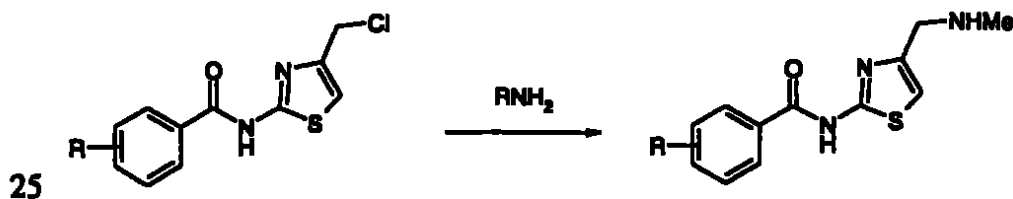
Other amide forming reactions include:

- 1a: Oxalyl chloride in the presence of a suitable solvent or base;
 1b: coupling reagents such as HATU or EDAC in the presence of a suitable solvent or base; and
 15 1c: POCl₃/Pyridine, according to Dirk T.S. Rijkers, Hans P.H.M. Adams, H. Coenraad Hemker, Godefridus I. Tesser, Tetrahedron, 1995, 51(41), pp11235-11250.

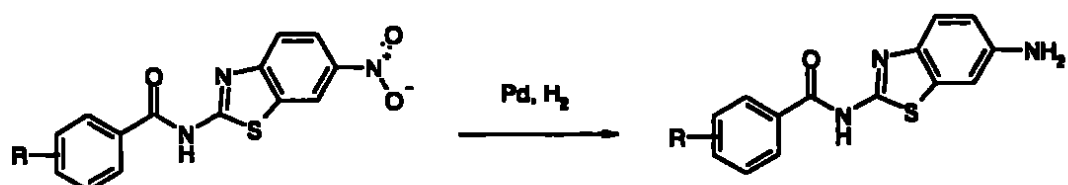
Route 2a and 2b



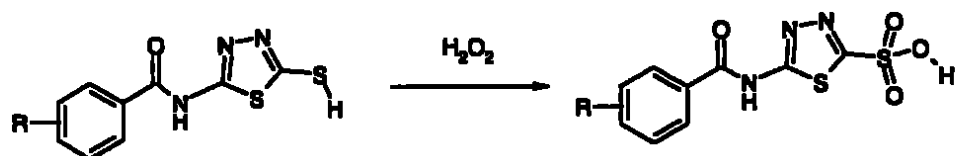
Route 3



Route 4

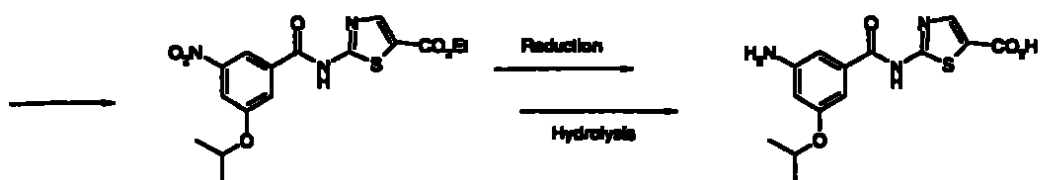
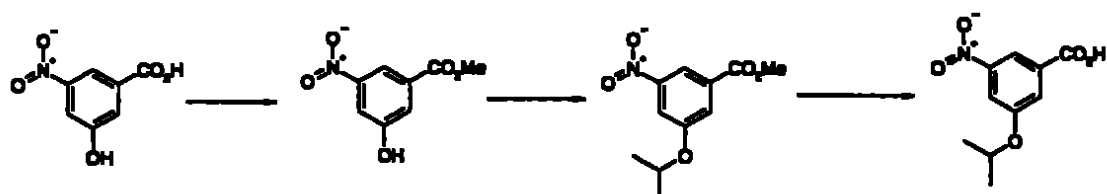
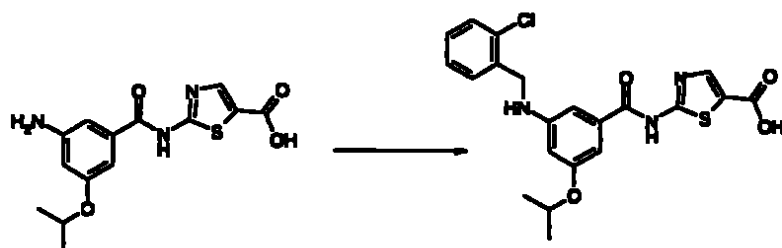


5 Route 5



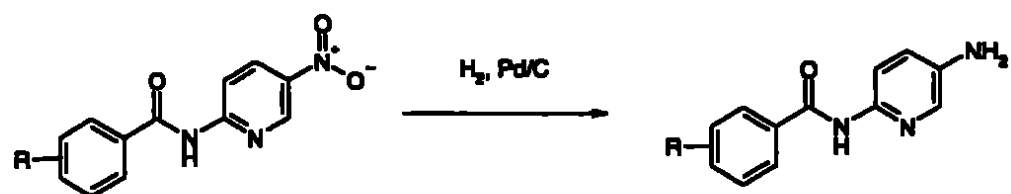
Route 6

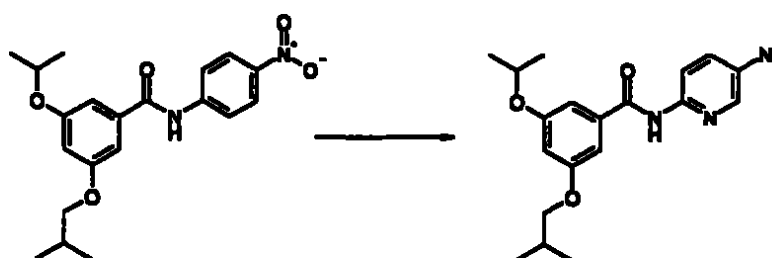
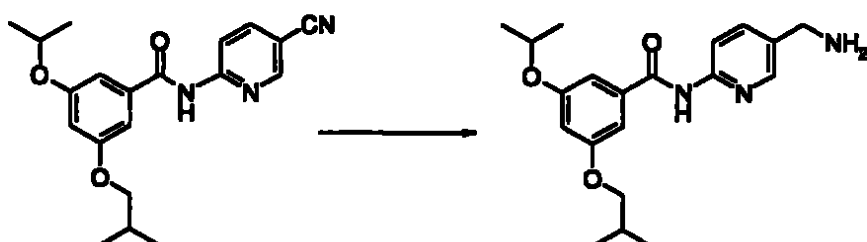
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Route 7

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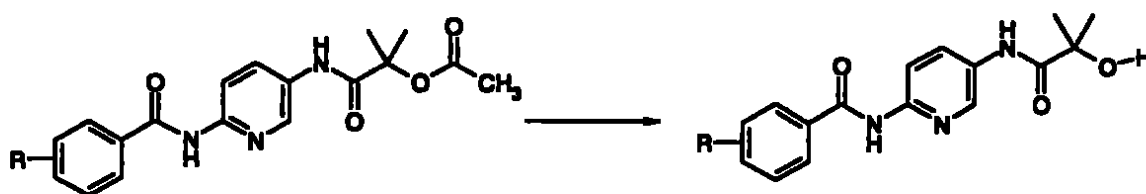


Route 7b:**5 Route 7c:****Route 8**

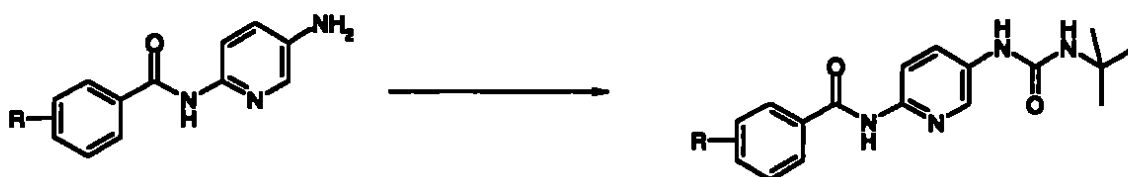
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**Route 9**

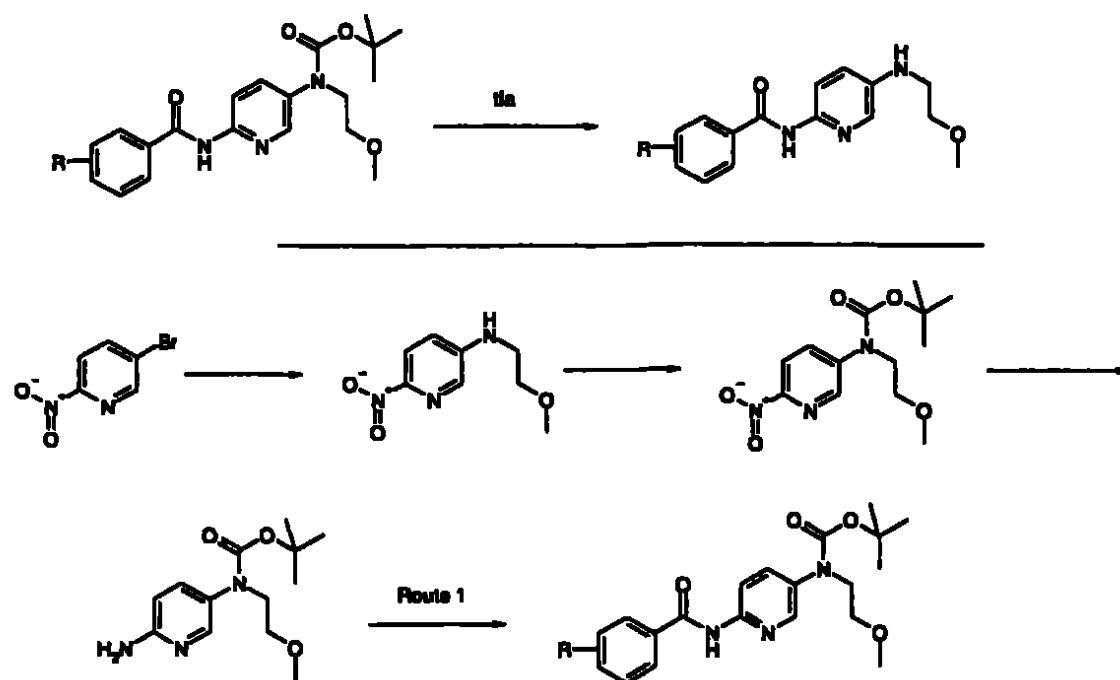
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**Route 10**

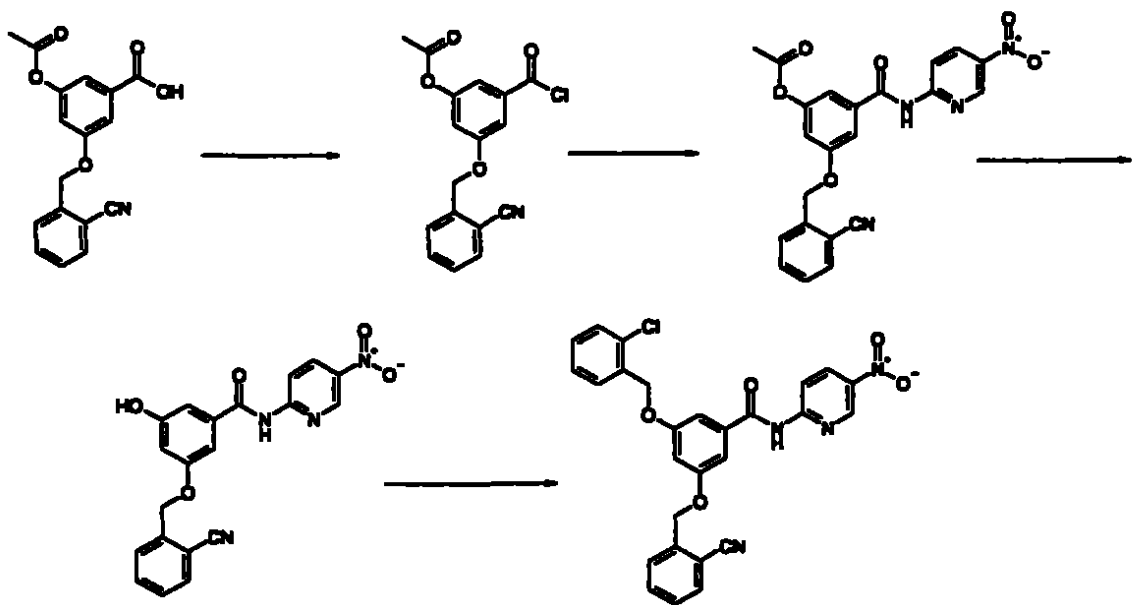
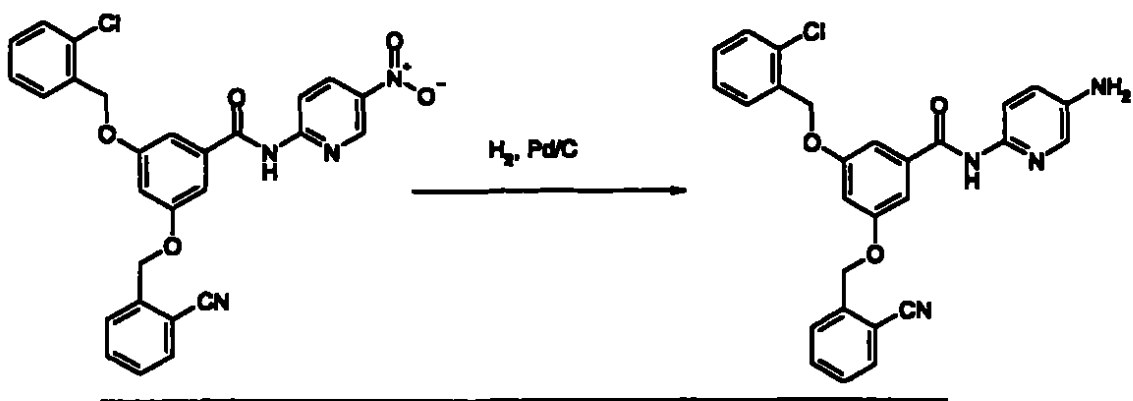
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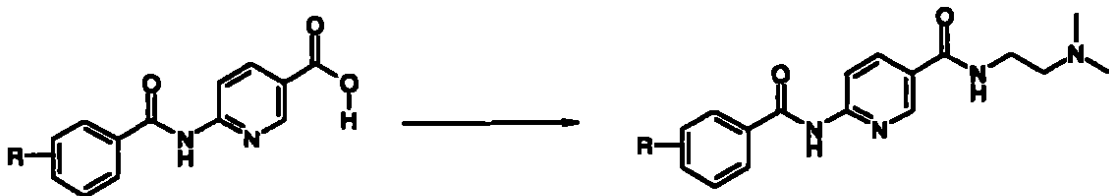
Route 11

Route 12



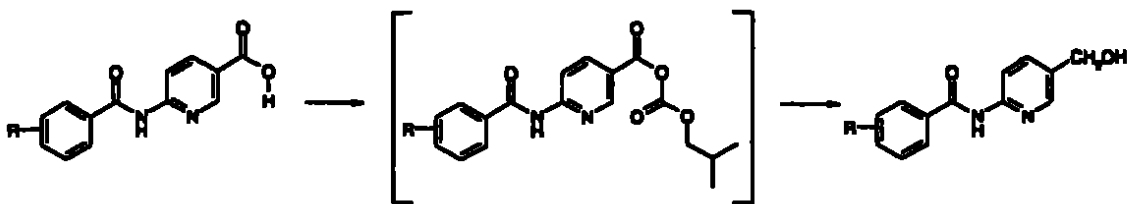
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Route 13



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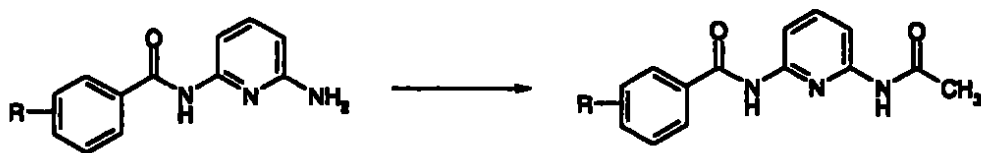
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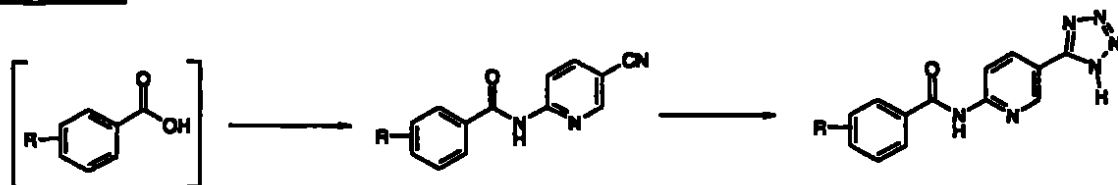
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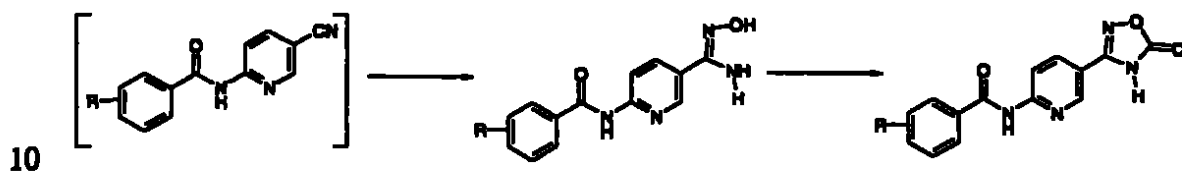
Route 15



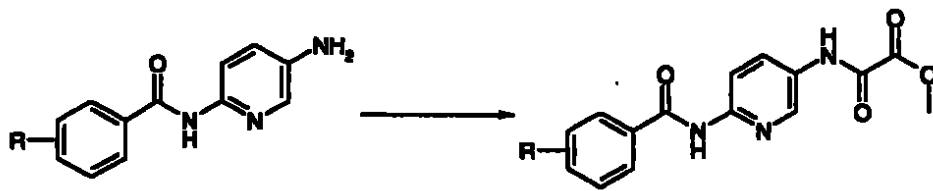
5 Route 16



Route 17

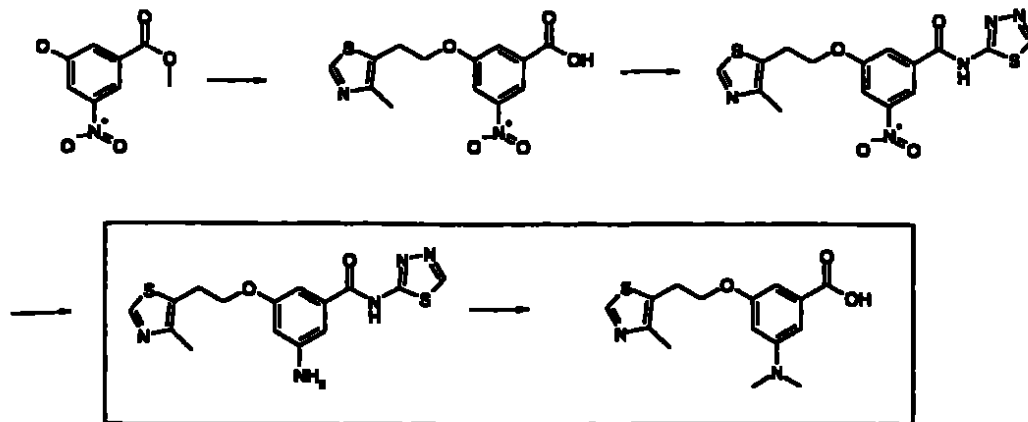


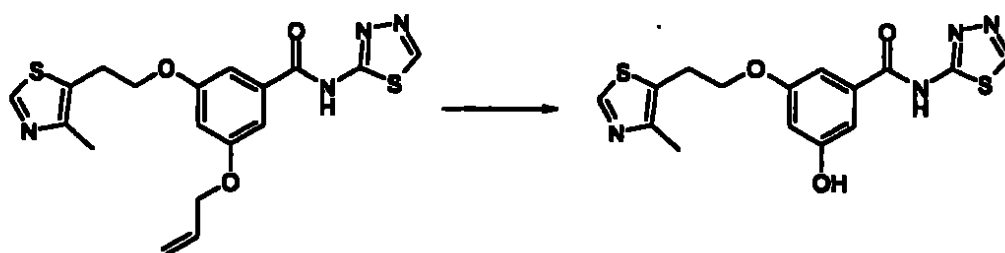
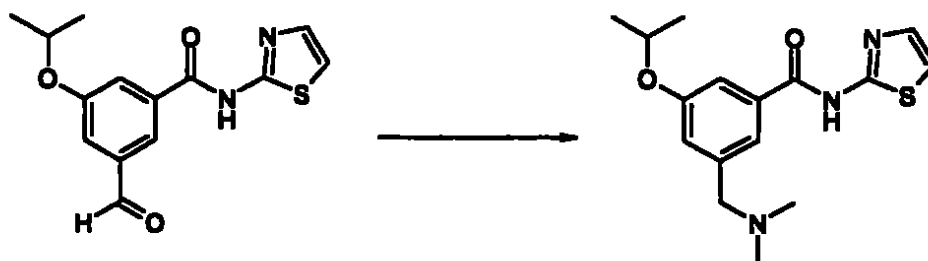
Route 18



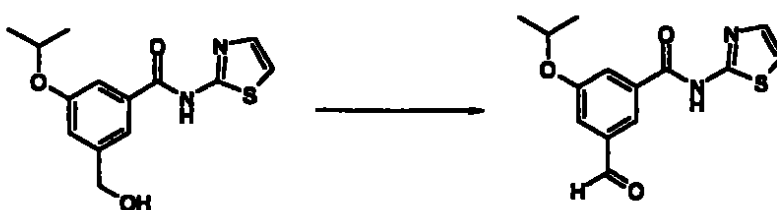
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Route 19:

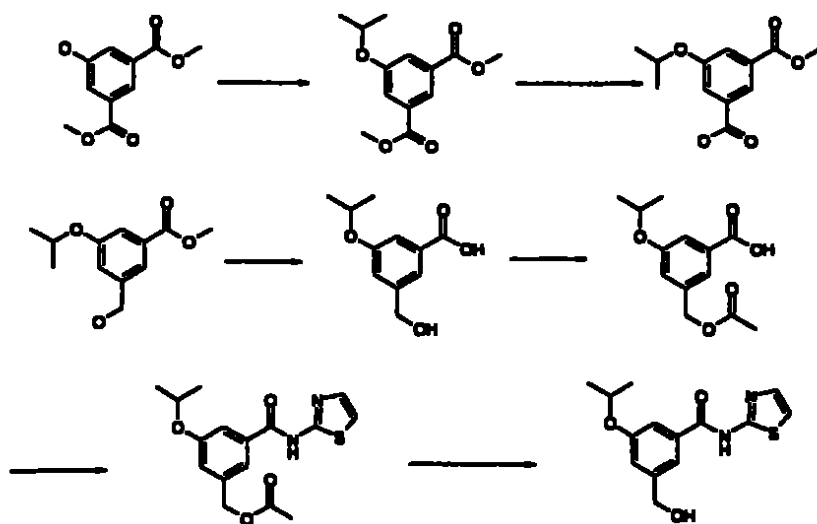


Route 20:**5 Route 21:****Route 22:**

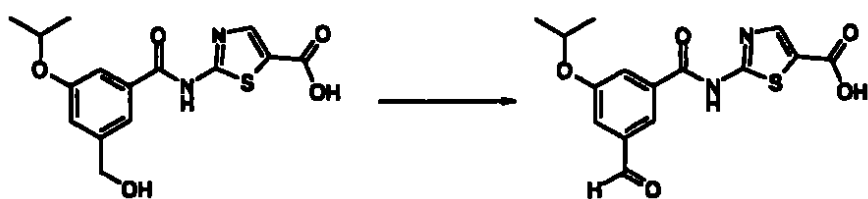
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**Route 23:**

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Route 24:

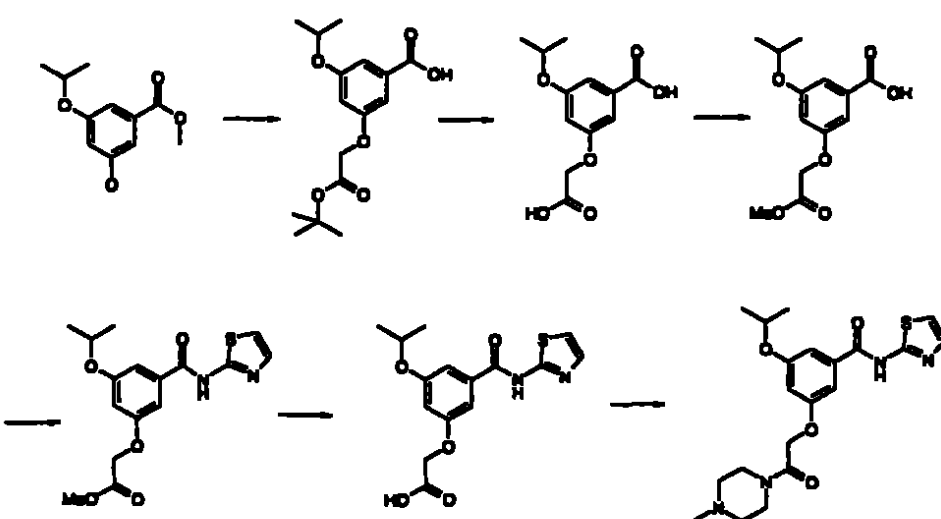


Route 25:



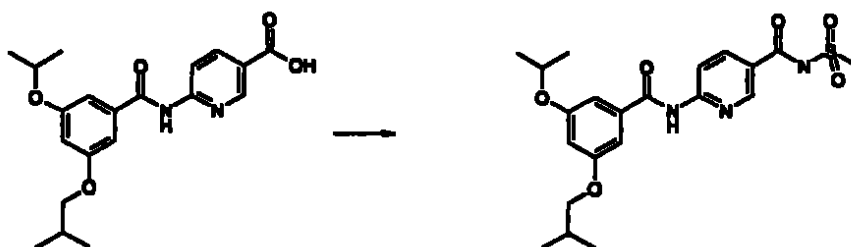
Route 26:

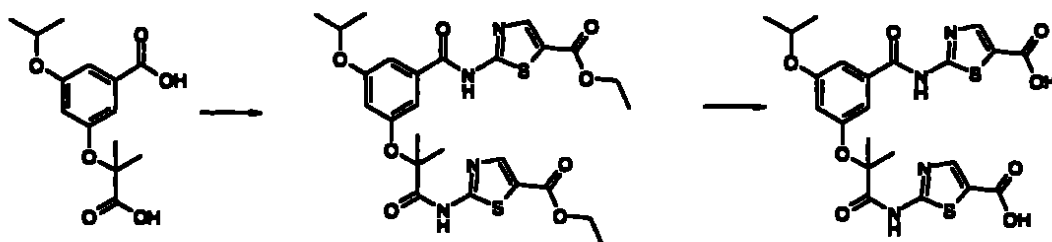
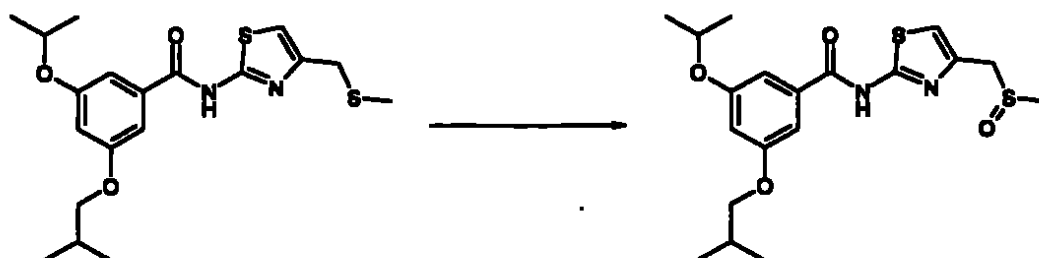
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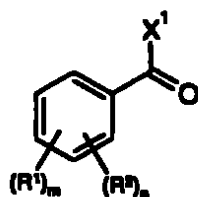
Route 27:

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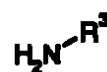


Route 28:**5 Route 29:**

Processes for the synthesis of compounds of Formula (I) are provided as a further
 10 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) which comprises:
 (a) reaction of a compound of Formula (IIIa) with a compound of Formula (IIIb),

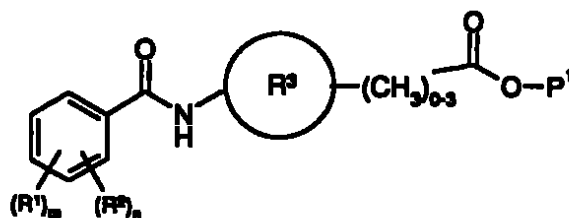


Formula (IIIa)



Formula (IIIb); or

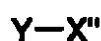
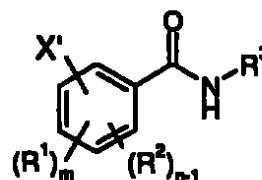
15 wherein X^1 is a leaving group
 (b) for compounds of Formula (I) wherein R^3 is substituted with $-(CH_2)_{0-3}COOH$,
 de-protection of a compound of Formula (IIIc),



Formula (IIIc)

20 wherein P^1 is a protecting group;

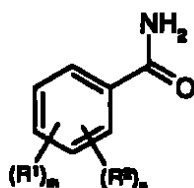
(c) for compounds of Formula (I) wherein n is 1, 2, 3 or 4, reaction of a compound of Formula (III_d) with a compound of Formula (III_e),

Formula (III_d)Formula (III_e)

5 wherein X' and X'' comprises groups which when reacted together form the group X ;

(d) for a compound of Formula (I) wherein n is 1, 2, 3 or 4 and X or X^1 is $-SO-Z-$ or $-SO_2-Z-$, oxidation of the corresponding compound of Formula (I) wherein X or X^1 respectively is $-S-Z-$;

(e) reaction of a compound of Formula (III_f) with a compound of Formula (III_g),

Formula (III_f)Formula (III_g); or

wherein X^2 is a leaving group

and thereafter, if necessary:

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

15 ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate thereof.

Specific reaction conditions for the above reactions are as follows:

Process a) – as described above for Route 1);

Process b) – as described above for Route 2);

20 *Process c)* – examples of this process are as follows:

- (i) to form a group when X is $-O-Z-$, X' is a group of formula $HO-Z-$ and X'' is a leaving group (alternatively X' is a group of formula L^2-Z- wherein L^2 is a leaving group and X'' is a hydroxyl group), compounds of Formula (III_d) and (III_e) are 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 100°C, optionally using metal catalysis such as palladium on carbon or cuprous iodide;

- (ii) to form a group when X is $N(R^6)-Z-$, X' is a group of formula $H-(R^6)N-Z-$ and X'' is a leaving group (alternatively X' is a group of formula L^2-Z- wherein L^2 is a leaving group and X'' is a group or formula $-N(R^6)-H$), compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as THF, an alcohol or acetonitrile, using a reducing agent such as sodium cyano borohydride or sodium trisacetoxyborohydride at room temperature;
- (iii) to form a group when X is $-SO_2N(R^6)-Z-$, X' is a group of formula $H-N(R^6)-Z-$ wherein L^2 is a leaving group and X'' is an activated sulphonyl group such as a group of formula $-SO_2-Cl$, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as methylene chloride, THF or pyridine, in the presence of a base such as triethylamine or pyridine at room temperature;
- (iv) to form a group when X is $-N(R^6)SO_2-Z-$, X' is an activated sulphonyl group such as a group of formula $Cl-SO_2-Z-$ group and X'' is a group of formula $-N(R^6)-L^2$ wherein L^2 is a leaving group, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as methylene chloride, THF or pyridine, in the presence of a base such as triethylamine or pyridine at room temperature;
- (v) to form a group when X is $-C(O)N(R^6)-Z-$, X' is a group of formula $H-N(R^6)-Z-$ wherein L^2 is a leaving group and X'' is an activated carbonyl group such as a group of formula $-C(O)-Cl$, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as THF or methylene chloride, in the presence of a base such as triethylamine or pyridine at room temperature;
- (vi) to form a group when X is $-N(R^6)C(O)-Z-$, X' is an activated carbonyl group such as a group of formula $Cl-C(O)-Z-$ group and X'' is a group of formula $-N(R^6)-L^2$ wherein L^2 is a leaving group, compounds of Formula (III_d) and (III_e) are reacted together in a suitable solvent such as THF or methylene chloride, in the presence of a base such as triethylamine or pyridine at room temperature;
- (vii) to form a group when X is $-CH=CH-Z-$, a Wittig reaction or a Wadsworth-Emmians Horner reaction can be used. For example, X' terminates in an aldehyde group and $Y-X''$ is a phosphine derivative of the formula $Y-CH-P^+PH_3$ which can be reacted together in a strong base such as sodium hydride or potassium *tert*-butoxide, in a suitable solvent such as THF at a temperature between room temperature and 100°C.

Process d) - the oxidization of a compound of Formula (I) wherein X or X¹ is -S-Z- is well known in the art, for example, reaction with metachloroperbenzoic acid (MCPBA) is the presence of a suitable solvent such as dichloromethane at ambient temperature. If an excess of MCPBA is used a compound of Formula (I) wherein X is —S(O₂)— is obtained.

- 5 *Process e)* - reaction of a Formula (III_f) with a compound of Formula (III_g) 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 100°C, optionally using metal catalysis, such as palladium on carbon or cuprous iodide.

During the preparation process, it may be advantageous to use a protecting group for a
10 functional group within R². 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
15 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.

- 20 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.
25 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
30 (2-6C)alkenyl groups (e.g. allyl and vinyloethyl).

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

Examples of hydroxy protecting groups include 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); 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. methylenedene); benzylenedene and substituted benzylenedene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base, metal- or enzymically-catalysed hydrolysis, or photolytically for groups such as *o*-nitrobenzyloxycarbonyl, or with fluoride ions for silyl groups.

Examples of protecting groups for amide groups include aralkoxymethyl (e.g. benzyloxymethyl and substituted benzyloxymethyl); alkoxymethyl (e.g. methoxymethyl and trimethylsilyloxymethyl); tri alkyl/arylsilyl (e.g. trimethylsilyl, *t*-butyldimethylsilyl, *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.

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:

5 (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
10 attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) 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,

15 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) chromatography was performed on silica (Merck Silica gel 60, 0.040 - 0.063
20 mm, 230 - 400 mesh); and

(vi) Biotage cartridges refer to pre-packed silica cartridges (from 40g up to 400g), eluted using a biotage pump and fraction collector system; Biotage UK Ltd, Hertford, Herts, UK.

25 Abbreviations

ADDP	azodicarbonyl)dipiperidine;
DCM	dichloromethane;
DEAD	diethyldiazocarboxylate;
DIAD	di-i-propyl azodicarboxylate;
30 DIPEA	di-isopropylethylamine
DMSO	dimethyl sulphoxide;
DMF	dimethylformamide;

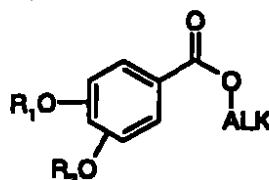
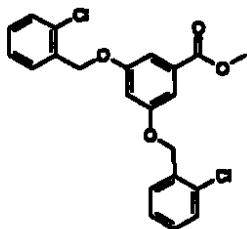
- 48 -

DtAD	di-t-butyl azodicarboxylate;
EDAC/EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride;
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate;
LCMS	liquid chromatography / mass spectroscopy;
MPLC	medium pressure liquid chromatography;
RT	room temperature; and
THF	tetrahydrofuran.

10

Generic Methods for alkylation of mono- and di-hydroxy benzoate esters:

The following generic alkylation methods are referred to in the Examples below.

**Generic Method A – synthesis of symmetrical diethers (R1 = R2)**

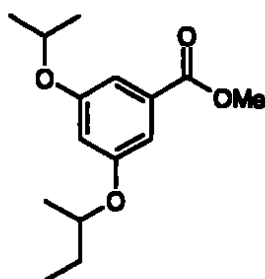
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Compound (a)

Methyl 3,5-dihydroxybenzoate (74.1g, 0.44M) was dissolved in dimethylformamide (400ml), potassium carbonate (152g, 1.10M) added, stirred for 15mins then 2-chlorobenzylchloride (117ml, 0.92M) added and heated at 100°C under an argon atmosphere. After 3hrs the reaction mixture was cooled to ambient temperature, concentrated *in vacuo*, diluted with water (800ml), extracted with ethyl acetate (2x600ml). The organic extracts were washed with brine (300ml), dried (MgSO₄), filtered, concentrated *in vacuo* to yield a brown oil which was triturated with diethyl ether/ isohexane to give compound (a) as an off-white solid (195g, 100%); ¹H nmr (d₆-DMSO, δ values): 3.81 (3H, s); 5.18 (4H, s); 6.98 (1H, m); 7.16 (1H, d); 7.36 (4H, m); 7.50 (2H, m); 7.58 (2H, m).

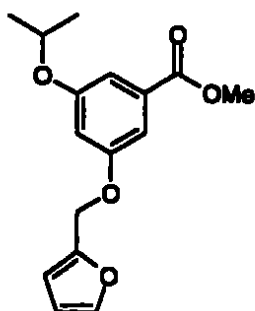
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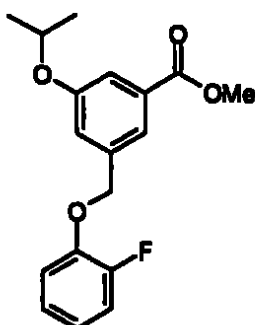
Generic Method B – synthesis of unsymmetrical diethers (R1 $\neq$ R2)

Compound (b)

- Methyl 3,5-dihydroxybenzoate (16.8g, 0.1mol) was dissolved in dimethylformamide (180ml), powdered potassium carbonate (27.6g, 0.2mol) added, followed by 2-iodopropane (10ml, 0.1mol), and the resulting suspension stirred overnight at ambient temperature under an argon atmosphere. The reaction mixture was diluted with water (1l) and extracted with diethyl ether (2x200ml). The organic extracts were washed sequentially with water and brine, dried (MgSO₄), filtered and concentrated *in vacuo* to yield a pale golden oil which was triturated with toluene and filtered to remove unreacted ether starting material. The filtrate was concentrated *in vacuo* and the residue chromatographed (2x90g Biotage cartridges, eluting with isohexane containing ethyl acetate (10% v/v increasing to 15% v/v) to give methyl 3-hydroxy 5-isopropoxy benzoate as a colourless solid (5.3g, 25%); ¹H nmr (d6-DMSO, δ values): 1.2 (6H, d); 3.8 (3H, s); 4.6 (1H, hept); 6.55 (1H, m); 6.85 (1H, m); 6.95 (1H, m); 9.8 (1H, s).
- Methyl 3-hydroxy 5-isopropoxy benzoate (1.5g, 7.2mmol) was dissolved in dimethylformamide (10ml), potassium carbonate (2.5g, 18mmol) added, followed by 2-bromobutane (1.2ml, 11mmol), and the resulting suspension stirred for 7 hours at 80 deg C under an argon atmosphere. The reaction mixture was cooled to ambient temperature, diluted with hexane / ethyl acetate (1:1 v/v) and washed sequentially with water and brine, dried (MgSO₄), filtered and concentrated *in vacuo* to yield a colourless oil which was chromatographed (flash column on silica (20g), eluting with isohexane containing ethyl acetate (5 % v/v) to give methyl 3-(2-butyloxy) 5-isopropoxy benzoate as a colourless oil (1.06g); ¹H nmr (d6-DMSO, δ values): 0.9 (3H, t); 1.2 (3H, d + 6H, d); 1.6 (2h, m); 3.85 (3H, s); 4.4 (1H, hept); 4.55 (1H, hept); 6.7 (1H, m); 7.0 (2H, m); m/z 267 (M+H)+.

Generic Method C – synthesis of unsymmetrical diethers (R1 $\neq$ R2):**Compound (c)**

Methyl 3-hydroxy 5-isopropoxy benzoate (0.5g, 2.4mmol) was dissolved in dichloromethane (10ml) and cooled to 0 deg C whilst stirring under an argon atmosphere; the solution was treated sequentially with triphenyl phosphine (Polymer supported, 1.19g, 3.6mmol), furfuryl alcohol (0.23 ml, 2.7 mmol) and di-*t*-butyl azodicarboxylate (DtAD, 0.082g, 3.5 mmol) added dropwise in dichloromethane (4ml), and the resulting solution stirred for 1.5 hours. The reaction was monitored by hplc and further reagents were added until the starting phenol was consumed – total reagents added were triphenyl phosphine (Polymer supported, 2.38g, 3 eq), furfuryl alcohol (0.53 ml, 2.5 eq) and DtAD (1.64g, 3 eq). The reaction mixture was concentrated *in vacuo* and purified by chromatography (flash column on silica, eluting with isohexane containing ethyl acetate (5 % v/v) to give methyl 3-(2-furyl methoxy) 5-isopropoxy benzoate as a colourless oil, (0.225g); ¹H nmr (d₆-DMSO, δ values): 1.25 (6H, d); 3.85 (3H, s); 4.65 (1H, hept); 5.1 (2H, s); 6.45 (1H, m); 6.6 (1H, m); 6.85 (1H, m); 7.05 (1H, m); 7.15 (1H, m) 7.75 (1H, m).

Generic Method D – synthesis of unsymmetrical diethers:**Compound (d)**

Di-*i*-propyl azodicarboxylate (DIAD, 0.74ml, 3.7 mM) was added to methyl (5-isopropoxy-3-methanol)-benzoate (0.56g, 2.5 mM), triphenylphosphine (0.98g, 3.7 mM) and 2-fluorophenol (0.24ml, 2.7 mM) in DCM (40ml) under argon at ambient temperature. After 10 mins concentrated, purified on silica gel (10-15%EtOAc/iso-hexane) gave the title compound as a

pale yellow oil, which solidified under high-vacuum (0.71g, 90%); ^1H NMR δ (d_6 -DMSO): 1.26 (d, 6H), 3.82 (s, 3H), 4.64 (m, 1H), 5.21 (s, 2H), 6.92 (m, 1H), 7.09 (m, 1H), 7.16-7.26 (m, 3H), 7.35 (s, 1H), 7.58 (s, 1H).

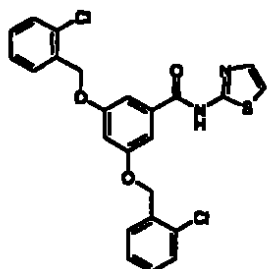
- 5 The above generic methods are for illustration only; it will be appreciated that alternative conditions that may optionally be used include: use of alternative solvents (such as acetone or tetrahydrofuran), alternative stoichiometries of reagents, alternative reaction temperatures and alternative methods of purification.

All analytical data (NMR and/or MS) were consistent with the proposed structures.

10

EXAMPLE A

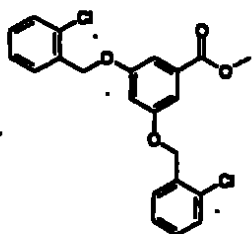
Route 1: 2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-thiazole



- Diisopropylethylamine (DIPEA, 0.34ml, 2.0mM) then *N,N*-dimethylaminopyridine (DMAP, 15 12mg, 0.1mM) were added to a solution of 2-aminothiazole (0.10g, 1.0mM) and 3,5-di-(2-chlorobenzoyloxy) benzoic acid chloride (0.42g, 1.0mM) in dichloromethane (10ml) under argon at ambient temperature. After 80mins the reaction mixture was filtered, washed with dichloromethane and dried under high vacuum to give the title compound as a colourless solid (0.20g, 41%); ^1H NMR δ (d_6 -DMSO): 5.24 (4H, s); 6.93 (1H, s); 7.26 (1H, d); 7.36-7.43 (6H, 20 m); 7.50 (2H, m); 7.55 (1H, d); 7.61 (2H, m); 12.60 (1H, br s).

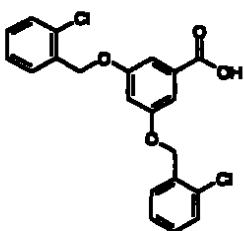
- Alternative conditions that may optionally be used include: use of an alternative solvent, such as tetrahydrofuran; use of pyridine as solvent, with or without the addition of DMAP or DIPEA; dissolving the acid chloride component in the solvent of choice, and adding the amine 25 component to it.

The requisite 3,5-Di-(2-chlorobenzoyloxy) benzoic acid chloride starting material, compound (c), was prepared as follows:



Compound (a)

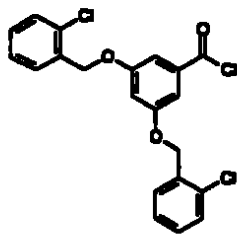
Methyl 3,5-dihydroxybenzoate (74.1g, 0.44M) was dissolved in dimethylformamide (400ml), potassium carbonate (152g, 1.10M) added, stirred for 15mins then 2-chlorobenzylchloride (117ml, 0.92M) added and heated at 100°C under an argon atmosphere. After 3hrs the
 5 reaction mixture was cooled to ambient temperature, concentrated *in vacuo*, diluted with water (800ml), extracted with ethyl acetate (2x600ml). The organic extracts were washed with brine (300ml), dried (MgSO₄), filtered, concentrated *in vacuo* to yield a brown oil which was triturated with diethyl ether/ isohexane to give compound (a) as an off-white solid (195g, 100%); ¹H nmr (d6-DMSO, δ values): 3.81 (3H, s); 5.18 (4H, s); 6.98 (1H, m); 7.16 (1H, d);
 10 7.36 (4H, m); 7.50 (2H, m); 7.58 (2H, m).



Compound (b)

2M Sodium hydroxide (700ml, 1.40M) was added to a solution of compound (a), methyl 3,5-di-(2-chlorobenzoyloxy) benzoate, (195g, 0.45M) in methanol (600ml)/ tetrahydrofuran
 15 (150ml) and stirred for 6hrs at 55°C. The organics were then removed *in vacuo*, acidified to pH 3-4 with concentrated hydrochloric acid, the precipitate filtered, washed with water and dried under high-vacuum at 60°C. Compound (b) was obtained as a colourless solid (.2/3NaCl) (199g, 100%); ¹H nmr (d6-DMSO, δ values): 5.18 (4H, s); 6.93 (1H, m); 7.15 (1H, d); 7.37 (4H, m); 7.49 (2H, m); 7.58 (2H, m).

20

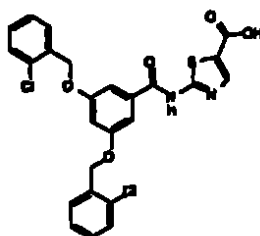


Compound (c)

Oxalyl chloride (7.91ml, 91mM) was added to a suspension of compound (b), 3,5-di-(2-chlorobenzoyloxy) benzoic acid.2/3NaCl (18.3g, 45.4mM) in dichloromethane (500ml) containing dimethylformamide (4 drops) under argon at ambient temperature. After 16 hrs the reaction mixture was filtered under argon, concentrated *in vacuo* then azeotroped with toluene (2x) to give the title compound as an off-white solid (17.5g, 100%); ¹H nmr (d₆-DMSO, δ values): 5.18 (4H, s); 6.94 (1H, m); 7.16 (1H, d); 7.35 (4H, m); 7.50 (2H, m); 7.58 (2H, m).

EXAMPLE B

Route 2a: 2-[3,5-di-(2-chlorobenzoyloxy)benzoyl] aminothiazole-5-carboxylic acid



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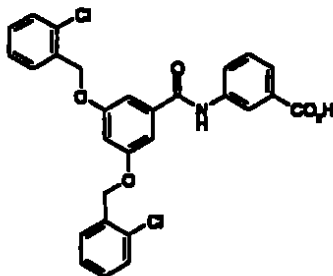
A solution of ethyl 2-[3,5-di-(2-chlorobenzoyloxy)benzoyl] aminothiazole-5-carboxylate (158mg, 0.28 mmol) in THF (2 ml) was treated with sodium hydroxide solution (0.57 ml of 2M, 1.4 mmol), and the reaction stirred at 40 - 50 deg C, until complete hydrolysis was achieved (with tlc monitoring, approximate reaction time 2hrs). The resulting solution was cooled, diluted with water (5 ml) and acidified to pH1 using c.HCl. The precipitate thus formed was filtered off, washed (water) and dried to give the title compound as a colourless solid, 130mg, ¹H NMR δ (d₆-DMSO): 5.25 (4H, s); 7.0 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H,m); 8.2 (1H, d).

The requisite starting material was prepared by a route analogous to that given in Example A.

20

EXAMPLE C

Route 2b: [3,5-di-(2-chlorobenzoyloxy)benzoyl] aminobenzene-3-carboxylic acid

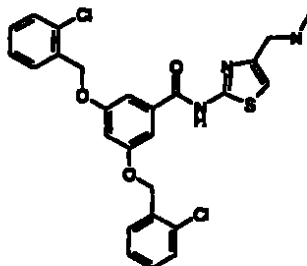


A suspension of methyl [3,5-di-(2-chlorobenzoyloxy)benzoyl] aminobenzene-3-carboxylate (455mg, 1.04 mmol) in THF was treated with sodium hydroxide solution (0.85 ml of 2M, 1.7 mmol), and the reaction stirred at ambient temperature, with tlc monitoring. Methanol (3 drops) and further additions of sodium hydroxide solution (2 x 0.85 ml of 2M, 3.4 mmol) were made, until complete hydrolysis was achieved. The resulting solution was diluted with water (30 ml) and acidified to pH1 (2M HCl); the precipitate thus formed was filtered off, washed (water) and dried to give the title compound as a colourless solid, 328mg, ¹H NMR δ (d₆-DMSO): 5.25 (4H, s); 7.0 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H,m); 8.2 (1H, d).

10 The requisite methyl ester starting material was prepared by a method analogous to that given in Example A.

EXAMPLE D

Route 3: 2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl] amino-4-methyl aminomethyl thiazole



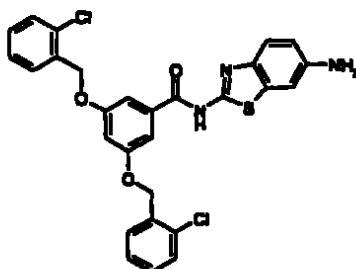
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2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-4-chloromethylthiazole (56mg, 0.10mM) was dissolved in 33% methylamine in methylated spirit (4ml) and stirred at ambient temperature for 16hrs. The reaction mixture was concentrated *in vacuo*, triturated with methanol, filtered and dried under high-vacuum to give the title compound as a colourless solid (30mg, 57%); ¹H nmr (d₆-DMSO, δ values): 2.63 (3H, m); 4.16 (2H, m); 5.24 (4H, s); 6.99 (1H, s); 7.38-7.44 (7H, m); 7.52 (2H, m); 7.62 (2H, m); 9.06 (1H, br s); 12.75 (1H, br s).

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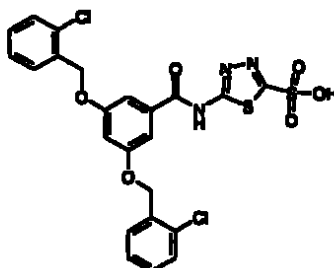
2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-4-chloromethylthiazole was prepared from 3,5-di-(2-chlorobenzoyloxy) benzoyl chloride (prepared according to the method described in Example A) and 2-amino 4-chloromethyl-thiazole (JACS, 1946, 68, 2155; prepared by route 1 described in Example A).

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K**EXAMPLE E****Route 4: 2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-6-aminobenzothiazole**

2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-6-nitrobenzothiazole (235mg, 0.40mM) was dissolved in ethyl acetate (40ml), ethanol (20ml) and dimethylformamide (5ml). 5% Palladium on carbon (46mg) was added under an argon atmosphere then the reaction mixture stirred under a hydrogen atmosphere for 16hrs. The reaction mixture was filtered through celite, concentrated *in vacuo*, triturated with methanol to give the title compound as a pale yellow solid (140mg, 63%); ¹H nmr (d6-DMSO, δ values): 5.19 (2H, br s); 5.23 (4H, s); 6.72 (1H, dd); 6.93 (1H, m); 7.03 (1H, m); 7.35-7.44 (7H, m); 7.51 (2H, m); 7.61 (2H, m); 12.46 (1H, br s).

2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-6-nitrobenzothiazole was prepared from 3,5-di-(2-chlorobenzoyloxy) benzoyl chloride (prepared according to the method described in Example A) and 2-amino-6-nitrobenzothiazole (prepared by route 1 described in Example A). ¹H nmr (d6-DMSO, δ values): 5.27 (4H, s); 7.03 (1H, s); 7.38-7.46 (4H, m); 7.49-7.55 (4H, m); 7.65 (2H, m); 7.93 (1H, d); 8.30 (1H, dd); 9.09 (1H, m); 13.28 (1H, br s).

EXAMPLE F**Route 5: 5-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-[1,3,4]thiadiazole-2-sulfonic acid**

5-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-[1,3,4]thiadiazole-2-thiol (200mg, 0.38mM) was suspended in 2M NaOH (5ml), cooled (ice bath) and 30% aqueous hydrogen peroxide (0.16ml, 1.54mM) added dropwise then allowed to warm to ambient temperature. After 40hrs

the reaction mixture was filtered, washed with water then methanol and dried under high-vacuum to give the title compound as a colourless solid (122mg, 57%); ¹H nmr (d₆-DMSO, δ values): 5.20 (4H, s); 6.68 (1H, m); 7.37 (4H, m); 7.45 (2H, m); 7.50 (2H, m); 7.62 (2H, m). MS (M-H⁺)⁻ 564, 566.

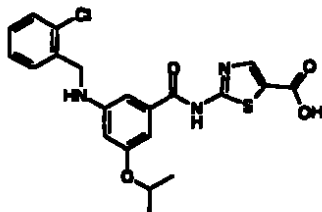
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5-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino-[1,3,4]thiadiazole-2-thiol was prepared from 3,5-di-(2-chlorobenzoyloxy) benzoyl chloride and 5-amino-[1,3,4]thiadiazole-2-thiol (Maybridge) by route 1 as described in Example A. ¹H nmr (d₆-DMSO, δ values): 5.21 (4H, s); 6.98 (1H, m); 7.34-7.40 (6H, m); 7.50 (2H, m); 7.59 (2H, m). MS (M-H⁺)⁻ 516, 518.

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EXAMPLE G

Route 6: 2-[(3-isopropoxy-5-(2-chlorobenzylamino)benzoyl)amino]-5-thiazolecarboxylic acid

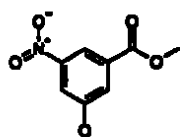


- 15 2-Chlorobenzaldehyde (0.012ml, 0.11mM) was added to 2-[(3-isopropoxy-5-aminobenzoyl)amino]-5-thiazolecarboxylic acid (29mg 0.09mM) and 4A molecular sieves (90mg) in methanol under an inert atmosphere at room temperature. After 1 hr sodium cyanoborohydride (7mg, 0.11mM) was added and the reaction mixture stirred for 16 hrs. The reaction mixture was filtered, concentrated *in vacuo*, the residue stirred with water then
- 20 extracted with ethyl acetate (3x10ml). The organic extracts were washed with brine (20ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give the title compound as a pale yellow solid (22mg, 55%); ¹H nmr (d₆-DMSO, δ values): 1.22 (6H, d); 4.36 (2H, m); 4.58 (1H, m); 6.24 (1H, s); 6.47 (1H, m); 6.84 (2H, m); 7.26 (3H, m); 7.37 (2H, m); 7.45 (1H, m); 7.76 (1H, br s). MS [M-CO₂H]⁻ 400, 402.

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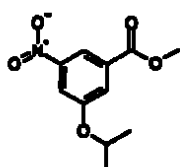
2-[(3-isopropoxy-5-aminobenzoyl)amino]-5-thiazolecarboxylic acid was prepared as follows:

33



Compound (d)

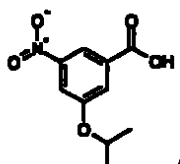
3-Nitro-5-hydroxy benzoic acid (6.1g, 33.3mM) was dissolved in methanol (150ml), concentrated sulfuric acid (2.0ml) was added, and the solution stirred at room temperature for 5 days. The reaction mixture was concentrated *in vacuo*, saturated aqueous sodium hydrogencarbonate (60ml) added cautiously and the aqueous layer extracted with ethyl acetate (200ml). The organic layer was washed with brine (80ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give compound (d) as a pale yellow solid (6.0g, 91%); ¹H nmr (d6-DMSO, δ values): 3.85 (3H, s); 7.67 (1H, m); 7.75 (1H, m); 8.05 (1H, m); 10.88 (1H, br s).



10

Compound (e)

2-Iodopropane (0.54ml, 5.4mM) was added to a solution of methyl 3-nitro-5-hydroxy benzoate (1.06g, 5.4mM) and potassium carbonate (1.12g, 8.1mM) in dimethylformamide (15ml) under an argon atmosphere at room temperature. The reaction mixture was heated at 60°C for 1hr then additional 2-iodopropane (0.32ml, 3.2mM) added and heating continued for a further 1hr. The reaction mixture was then concentrated *in vacuo*, water (50ml) and ethyl acetate (100ml) added. The organic layer was separated and washed with brine (40ml), dried (MgSO₄) filtered, concentrated *in vacuo* to give compound (e) as a mobile brown oil; ¹H nmr (d6-DMSO, δ values): 1.30 (6H, s); 3.90 (3H, s); 4.84 (1H, m); 7.76 (1H, m); 7.89 (1H, m); 8.16 (1H, m).

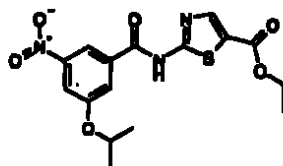


20

Compound (f)

2M Sodium hydroxide (12.3ml, 24.7mM) was added to a solution of methyl (3-nitro-5-isopropoxy) benzoic acid (1.18g, 4.9mM) in methanol (60ml) and stirred for 5hrs at room temperature. The reaction mixture was then concentrated *in vacuo*, acidified to pH 1-2 with 2M hydrochloric acid, the precipitate filtered, washed with water and dried under high-vacuum over silica gel. Compound (f) was obtained as an off-white solid (1.04g, 94%); ¹H

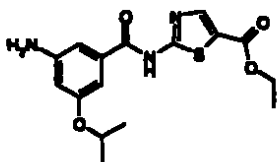
nmr (d6-DMSO, δ values): 1.30 (6H, s); 4.81 (1H, m); 7.74 (1H, m); 7.85 (1H, m); 8.14 (1H, m). MS ($M-H^+$)⁻ 224.



Compound (g)

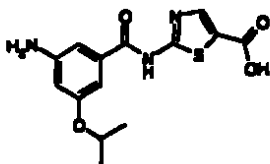
- 5 Oxalyl chloride (0.75ml, 8.6mM) was added to 3-nitro-5-isopropoxy benzoic acid (1.03g, 4.3mM) in dichloromethane (50ml) containing dimethylformamide (2 drops) under an argon atmosphere at room temperature. After 3hrs the reaction mixture was concentrated *in vacuo* and azeotroped with toluene to give an orange oil which was dissolved in dichloromethane (40ml). Ethyl 2-aminothiazole-5-carboxylate (0.89g, 5.1mM), diisopropylethylamine (1.77g, 10.3mM) and N,N-dimethylaminopyridine (50mg, 0.43mM) were added and stirred for 1hr under an argon atmosphere. After which the reaction mixture was concentrated *in vacuo* then the pale brown residue purified on silica gel using 15 to 20% ethyl acetate/isohexane as eluant. Compound (g) was obtained as a pale yellow solid (1.56g, 92%); ¹H nmr (d6-DMSO, δ values): 1.32 (6H, d); 4.88 (1H, m); 7.87 (1H, s); 8.05 (1H, s); 8.14 (1H, s); 8.45 (1H, s).

15



Compound (h)

- 10% Palladium on carbon (20mg) was added under an argon atmosphere to a solution of ethyl 2-[(3-isopropoxy-5-nitro)benzoylamino]-5-thiazolecarboxylate (209mg, 0.53mM) in ethyl acetate (35ml). Hydrogen gas was introduced and the reaction mixture stirred vigorously for 18hrs before filtering through celite and concentration *in vacuo* to give compound (h) as pale yellow solid (160mg, 83%); ¹H nmr (d6-DMSO, δ values): 1.25 (6H, d); 1.29 (3H, t); 4.28 (2H, q); 4.58 (1H, m); 5.31 (2H, br s); 6.33 (1H, m); 6.81 (1H, m); 6.87 (1H, s); 8.17 (1H, s).

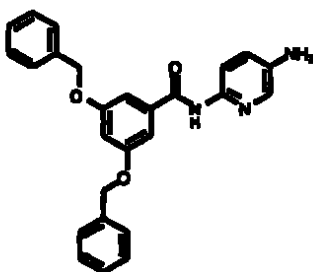


Compound (k)

2M Sodium hydroxide (0.3ml, 0.57mM) was added to a solution of ethyl 2-[(3-isopropoxy-5-amino)benzoylamino]-5-thiazolecarboxylate (40mg, 0.11mM) in tetrahydrofuran (1.2ml)/methanol (0.5ml) and heated at 50°C for 5hrs then at room temperature overnight. The reaction mixture was then concentrated *in vacuo*, acidified to pH 4-5 with 2M hydrochloric acid, the precipitate filtered, washed with water and dried under high-vacuum over silica gel. Compound (k) was obtained as a red-brown solid (35mg, 100%); ¹H nmr (d₆-DMSO, δ values): 1.27 (6H, d); 4.63 (1H, m); 6.58 (1H, s); 7.05 (1H, s); 7.16 (1H, s); 8.14 (1H, s).

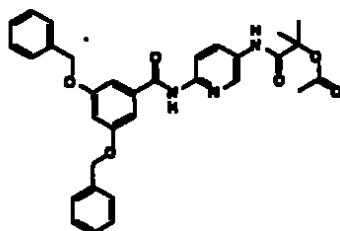
EXAMPLE H

10 Route 7: 2-[(3,5-dibenzyloxybenzoyl)amino]-5-aminopyridine

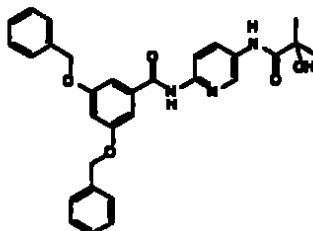


To a stirred solution of 2-[(3,5-dibenzyloxybenzoyl)amino]-5-nitropyridine (910 mg) in DMF (6 ml) was added Zinc dust (1300 mg) and a solution of ferric chloride hexahydrate (1700 mg) in water (6 ml). The resulting mixture was stirred at 120°C for three hours. Allowed to cool to ambient temperature. The mixture was extracted with ethyl acetate. The extract was washed with water (50 ml), brine (50 ml), dried over MgSO₄, then volatile material was removed by evaporation to leave a solid, which was dried under high vacuum for 24 hours at 100°C to give the title compound (518 mg) as a solid, ¹H NMR δ (d₆-DMSO): 5.17 (m, 6H), 6.80 (s, 1H), 7.00 (d, 1H), 7.26 to 7.46 (m, 12H), 7.71 (s, 1H), 7.78 (d, 1H), 10.28 (br s, 1H). MS ES⁺ 426.52 (M+H)⁺.

The requisite 6-[(3,5-dibenzyloxybenzoyl)amino]-3-nitropyridine starting material was prepared by a method analogous to that given in Example A (route 1), starting from 2-amino-5-nitropyridine; ¹H NMR δ (d₆-DMSO): 5.18 (s, 4H), 6.90 (s, 1H), 7.29-7.50 (m, 12H), 8.42 (d, 1H), 8.64 (d, 1H), 9.23 (s, 1H), 11.46 (brs, 1H). MS ES⁺ 456.12 (M+H)⁺.

EXAMPLE I**Route 8: *N*-{6-[3,5-dibenzyloxybenzoyl]amino}-pyridin-3-yl}-2-acetoxy-2-methyl-propionamide**

- 5 To a stirred solution of 2-[(3,5-dibenzyloxybenzoyl)amino]-5-aminopyridine (200 mg) in THF (2 ml) and pyridine (2 ml) was added a solution of 2-acetoxyisobutyryl chloride (98 mg) in THF (1 ml). The mixture was stirred at ambient temperature for 16 hours. Volatile material was removed by evaporation. The residue was dissolved in ethyl acetate (50 ml), washed with water (25 ml), brine (25 ml), dried over MgSO_4 . Volatile material was removed by
- 10 evaporation to leave a gum which was triturated under ether to give the title compound (211 mg) as a solid, ^1H NMR δ (d_6 -DMSO): 1.55 (s, 6H), 2.08 (s, 3H), 5.18 (s, 4H), 6.85 (s, 1H), 7.29 to 7.50 (m, 12H), 7.98 (dd, 1H), 8.13 (d, 1H), 8.61 (s, 1H), 9.70 (s, 1H), 10.72 (s, 1H). MS ES $^-$ 552.22 (M-H) $^-$.

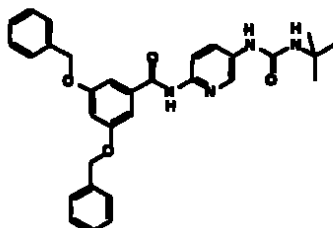
15 EXAMPLE I**Route 9: *N*-{6-[(3,5-dibenzyloxybenzoyl)amino]-pyridin-3-yl}-2-hydroxy-2-methyl-propionamide**

- To a stirred suspension of *N*-{6-[(3,5-dibenzyloxybenzoyl)amino]-pyridin-3-yl}-2-acetoxy-2-
- 20 methyl-propionamide (158 mg) in methanol (10 ml) was added a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (30 mg) in water (1 ml) and THF (3 ml). The mixture was stirred at ambient temperature for 20 hours. Volatile material was removed by evaporation. To the residue was added water (10 ml). Made acidic with 2M hydrochloric acid. Precipitate filtered off, washed with ethyl acetate, and dried under high vacuum to give the title compound (120 mg) as a solid, ^1H NMR δ (d_6 -

DMSO): 1.35 (s, 6H), 5.18 (s, 4H), 6.88 (s, 1H), 7.28 to 7.48 (m, 12H), 8.08 (d, 1H), 8.22 (d, 1H), 8.82 (s, 1H), 9.90 (s, 1H), 10.96 (s, 1H). MS ES⁺ 512.16 (M+H)⁺.

EXAMPLE K

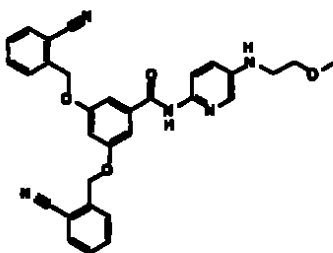
5 **Route 10: 3,5-dibenzoyloxy-N-(5-[(*tert*-butylamino)carbonyl]amino)pyridin-2-yl)benzamide**



A solution of *tert*-butyl isocyanate (51 mg) in THF (5 ml) was treated with 2-[(3,5-dibenzoyloxybenzoyl)amino]-5-aminopyridine (212 mg), and stirred at ambient temperature for 10 24 hours. More *tert*-butyl isocyanate (0.34 ml) added, and stirring continued at ambient temperature for a further 4 days. Volatile material was removed by evaporation and the residue was triturated under methanol to give the title compound (159 mg) as a solid, ¹H NMR δ (d₆-DMSO): 1.30 (s, 9H), 5.18 (s, 4H), 6.09 (s, 1H), 6.85 (s, 1H), 7.32 to 7.50 (m, 12H), 7.78 (dd, 1H), 8.04 (d, 1H), 8.38 (s, 1H), 8.44 (s, 1H), 10.65 (s, 1H). MS ES⁺ 525.61 15 (M+H)⁺.

EXAMPLE L

20 **Route 11: 3,5-di(2-cyanobenzoyloxy)-N-[5-(2-methoxyethyl)amino]pyridin-2-yl)benzamide**

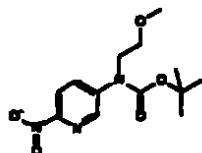


To a stirred solution of *tert*-butyl 6-[(3,5-di(2-cyanobenzoyloxy)benzoyl)amino]pyridin-3-yl(2-methoxyethyl)carbamate (237 mg) in dichloromethane (10 ml) was added trifluoroacetic acid (3 ml). The solution was stirred at ambient temperature for three hours. Volatile material was removed by evaporation. The residue was diluted in DCM (100 ml), washed with 2M sodium 25 Hydroxide (50 ml), brine (50 ml), dried over MgSO₄. Volatile material was removed by

evaporation to give the title compound (190 mg) as a foam, ^1H NMR δ (d_6 -DMSO): 3.22 (t, 2H), 3.28 (2, 3H), 3.50 (t, 2H), 5.31 (s, 4H), 6.92 (s, 1H), 7.12 (dd, 1H), 7.34 (s, 2H), 7.57 (m, 2H), 7.75 (m, 5H), 7.82 (d, 1H), 7.91 (d, 2H), 10.49 (br s, 1H). MS ES⁺ 534.41 (M+H)⁺.

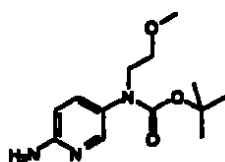
5 The requisite starting materials were prepared as follows:

Preparation of *tert*-butyl 2-nitropyridin-5-yl(2-methoxyethyl)carbamate



To a suspension of Cs_2CO_3 (1430 mg) in toluene was added 2-nitro-5-bromopyridine (406 mg), $\text{Pd}(\text{Ac})_2$ (44 mg), 1,1-bis(diphenylphosphino)ferrocene (322 mg) and 2-methoxyethyl
 10 amine (0.26 ml). The mixture was stirred at 85°C, under Nitrogen, for 16 hours. Allowed to cool to ambient temperature. Diluted with ethyl acetate (100 ml), and filtered through a celite plug. Volatile material was removed by evaporation, the residue was purified by flash chromatography on silica, eluted with 50-100% ethyl acetate in hexane to give a solid which was added to a solution of di-*tert*-butyl-dicarbonate (436mg) and *N*-dimethyl-aminopyridine
 15 (cat) in THF (10 ml). The solution was stirred for 14 hours at 75°C. Allowed to cool to ambient temperature, then the volatile material was removed by evaporation. The residue was dissolved in ethyl acetate (100 ml), washed with water (50 ml), brine (50 ml), dried over MgSO_4 . Volatile material was removed by evaporation, the residue was purified by flash chromatography on silica, eluted with 20-40% ethyl acetate in hexane to give the title
 20 compound (359 mg) as a gum, ^1H NMR δ (CDCl_3): 1.49 (s, 9H), 3.33 (s, 6H), 3.62 (t, 2H), 3.86 (t, 2H), 8.06 (dd, 1H), 8.21 (d, 1H), 8.65 (s, 1H). MS ES⁺ 298.35 (M+H)⁺.

Preparation of *tert*-butyl 2-aminopyridin-5-yl(2-methoxyethyl)carbamate

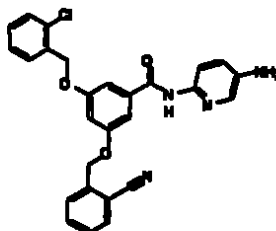


25 To a solution of *tert*-butyl 2-(6-nitropyridin-3-yl)-4-methoxybutanoate (350 mg) in ethanol (20 ml) and ethyl acetate (20 ml) was added 10 % Palladium on carbon (100 mg). The suspension was stirred at ambient temperature for 16 hours under Hydrogen. Filtered through celite, then volatile material removed by evaporation to give the title compound (299 mg) as a

solid, ^1H NMR δ (d_6 -DMSO): 1.32 (brs, 9H), 3.18 (s, 3H), 3.34 (t, 2H), 3.56 (t, 2H), 5.84 (s, 2H), 6.37 (d, 1H), 7.17 (dd, 1H), 7.70 (d, 1H). MS ES^+ 268.34 ($\text{M}+\text{H}^+$).

EXAMPLE M

5 Route 12: *N*-(5-aminopyridin-2-yl)-3-[(2-chlorobenzyl)oxy]-5-[(2-cyanobenzyl)oxy]benzamide

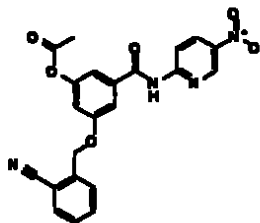


The title compound was prepared from *N*-(5-nitropyridin-2-yl)-3-[(2-chlorobenzyl)oxy]-5-[(2-cyanobenzyl)oxy]benzamide using a method similar to that described in Route 7.

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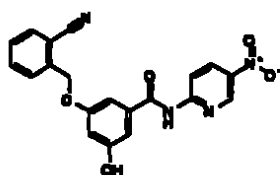
The requisite starting materials were prepared as follows:

Preparation of 3-[[[(5-nitropyridin-2-yl)amino]carbonyl]-5-[(2-cyanobenzyl)oxy]phenyl]acetate



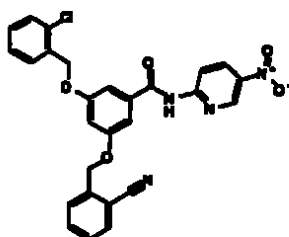
- 15 To a stirred solution of 3-acetoxy,5-(2-cyanobenzyl)oxybenzoic acid (8760 mg) in THF (100 ml) was added Oxalyl chloride (3.6 ml) and DMF (0.5 ml). The mixture was stirred at ambient temperature for 3 hours. Volatile material was removed by evaporation. The residue was dissolved in a mixture of THF (60 ml) and pyridine (40 ml). 2-amino-5-nitropyridine (3919 mg) added. The stirred mixture was heated to 55°C for 16 hours. Volatile material was
- 20 removed by evaporation to leave a gum which was purified by flash chromatography on silica eluted with 1-5% ethyl acetate in hexane to give the title compound (6200 mg) as a solid, ^1H NMR δ (d_6 -DMSO): 2.29 (s, 3H), 5.37 (s, 2H), 7.17 (s, 1H), 7.45 (s, 1H), 7.58 (m, 1H), 7.70 (s, 1H), 7.76 (m, 2H), 7.92 (d, 1H), 8.40 (d, 1H), 8.65 (dm, 1H), 9.21 (m, 1H), 11.57 (s, 1H). MS ES^+ 433.48 ($\text{M}+\text{H}^+$).

25

Preparation of *N*-(5-nitropyridin-2-yl)-3-[(2-cyanobenzyl)oxy]-5-hydroxybenzamide

A suspension of 3-[[5-(5-nitropyridin-2-yl)amino]carbonyl]-5-[(2-cyanobenzyl)oxy]phenyl acetate (5710 mg) in THF (35 ml) was treated with 25% NaOMe in methanol (6 ml). Stirred at ambient temperature for 30 minutes. Acidified with 2M hydrochloric acid (25 ml), then extracted with ethyl acetate (100 ml). The extract was washed with water (50 ml), brine (50 ml), dried over MgSO₄. Volatile material was removed by evaporation to give a solid. This was washed with hot methanol to give the title compound (4358 mg) as a solid, LCMS *rt* = 2.38 min (90.5%). ES⁺ 391.45 (M+H)⁺.

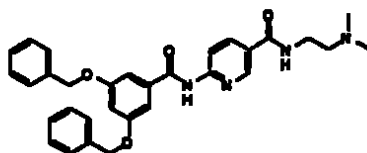
10

Preparation of *N*-(5-nitropyridin-2-yl)-3-[(2-chlorobenzyl)oxy]-5-[(2-cyanobenzyl)oxy]benzamide

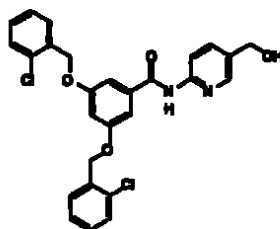
A solution of *N*-(5-nitropyridin-2-yl)-3-[(2-cyanobenzyl)oxy]-5-hydroxybenzamide (195 mg) in DMF (3 ml) was treated with Ag₂CO₃ (165 mg) and 2-Chlorobenzyl bromide (0.073 ml). Heated to 85°C and stirred for 17 hours under Nitrogen. Allowed to cool to ambient temperature. Water (25 ml) added. Extracted with ethyl acetate (50 ml), washed with brine (25 ml), dried over MgSO₄. Volatile material was removed by evaporation to give a solid, which was purified by flash chromatography on silica eluted with 0-5% ethyl acetate in dichloromethane to give the title compound (43 mg) as a solid, ¹H NMR δ (d₆-DMSO): 5.20 (s, 2H), 5.33 (s, 2H), 6.96 (s, 1H), 7.40 (m, 5H), 7.57 (m, 2H), 7.72 (m, 2H), 7.90 (d, 1H), 8.40 (d, 1H), 8.64 (dd, 1H), 9.22 (s, 1H), 11.50 (s, 1H). LCMS *rt* = 3.27 min (97.4%), ES⁺ 515.50 (M+H)⁺.

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37

EXAMPLE N**Route 13: 6-[(3,5-Di-(benzyloxy)benzoyl)amino]-N-[2-(dimethylamino)ethyl]nicotinamide**

- 5 Diisopropylethylamine (DIPEA, 0.23ml, 1.3mM) then 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDC, 126mg, 0.66mM) were added to a solution of 2-dimethylaminoethylamine (0.57ml, 0.53mM) and 6-[(3,5-Di-(benzyloxy)benzoyl)amino]nicotinic acid (0.20g, 0.44mM) in dichloromethane (10ml) under argon at ambient temperature. After 16 hours the reaction mixture was evaporated *in vacuo*
- 10 and then chromatographed on SiO₂ using a gradient elution of 10 to 25% methanol in dichloromethane. The fractions containing product were evaporated to give a cream solid (0.052g, 25%); ¹H NMR δ (d₆-DMSO): 2.67 (6H, s); 3.11 (2H, m); 3.62 (2H, m); 5.18 (4H, s); 6.88 (1H, s); 7.27-7.52 (12H, br m); 8.18-8.36 (2H, m); 8.90 (1H, s); 10.20 (1H, br s).

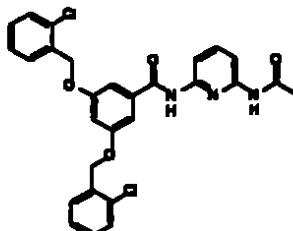
15 EXAMPLE O**Route 14: 2-[3,5-Di-(2-chlorobenzyloxy) benzoylamino]-5-hydroxymethyl pyridine**

- To a cold (-15 degC) solution of 2-[3,5-Di-(2-chlorobenzyloxy)benzoyl]amino-pyridine-5-carboxylic acid (305 mg, 0.59 mmol) in dimethoxy ethane (5ml) was added 4-methyl
- 20 morpholine (80μl, 1eq) and isobutyl chloroformate (76μl, 1.02 eq). The reaction mixture was stirred at -15deg C for 15 mins and then filtered; the residue was washed with dimethoxy ethane (5x1ml). The filtrate and washings were cooled to -15 deg C and treated with a suspension of sodium borohydride (22mg, 1eq) in water (1ml). After the effervescence had ceased, water (50ml) and ethyl acetate (30ml) were added; the reaction mixture was
- 25 evaporated to dryness and the residue absorbed onto silica. The required compound was isolated by flash chromatography (eluting with 5% methanol in dichloromethane) to give the

title compound as a colourless solid (97 mg), ^1H NMR δ (d_6 -DMSO): 4.5 (1H, d), 5.25 (s, 4H), 6.9 (s, 1H), 7.40 (m, 6H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (dd, 1H), 8.10 (d, 1H), 8.3 (s, 1H), 10.8 (br s, 1H); LCMS $\text{rt} = 3.25$ min (100%), ES^+ 509 ($\text{M}+\text{H}^+$).

5 EXAMPLE P

Route 15: N-[6-[3,5-di-(2-chlorobenzoyloxybenzoyl)amino]-pyridin-2-yl]-2-acetamide



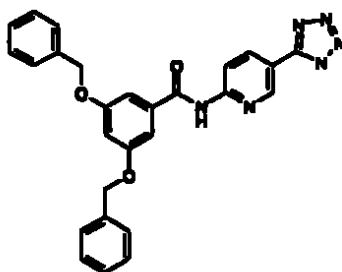
To a solution of 2-[(3,5-di-(2-chlorobenzoyloxybenzoyl)amino)-6-aminopyridine (220 mg, 0.45 mmol) in tetrahydrofuran (4 ml) was added pyridine (43 mg, 0.54 mmol) and acetyl chloride (42 mg, 0.54 mmol), and the reaction mixture stirred at ambient temperature for 16 hours. The reaction mixture was diluted with diethyl ether and washed successively with water, 1M citric acid, and water; the solution was dried over magnesium sulfate and the solvent removed *in vacuo* to give a yellow solid (154mg). Trituration with methanol gave the title compound (75mg), ^1H NMR δ (d_6 -DMSO): 3.3 (3H, s), 5.25 (s, 4H), 6.95 (s, 1H), 7.3 (d, 2H), 7.4 (m, 4H), 7.5 (m, 2H), 7.6 (m, 2H), 7.7 (m, 1H), 7.8 (m, 2H), 10.14 (br s, 1H), 10.36 (br s, 1H); ES^+ 536/538 ($\text{M}+\text{H}^+$).

The starting material, 2-[(3,5-di-(2-chlorobenzoyloxybenzoyl)amino)-6-aminopyridine, is exemplified herein as Example number 106.

20

EXAMPLE Q

Route 16: 3,5-bis(benzyloxy)-N-[5-(1H-tetrazol-5-yl)pyridin-2-yl]benzamide



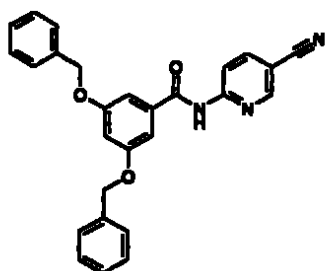
Tributyltin azide (156 μL , 0.57 mmol) was added to a suspension of 3,5-bis(benzyloxy)-N-(5-cyanopyridin-2-yl)benzamide (180 mg, 0.41 mmol) in toluene (3 mL). The mixture was

25

heated at reflux for 16 hours. The suspension was cooled and partitioned between ethyl acetate and hydrochloric acid (1M). The organic layer was concentrated in vacuo and the residue was purified by MPLC on silica MPLC (eluting with 1% methanol / DCM to 15% methanol / DCM). The tetrazole was obtained as a colourless solid (113 mg, 57%). ¹H NMR δ (d₆-DMSO): 5.19 (4H, s); 6.88 (1H, s); 7.26-7.48 (12H, m); 8.40 (1H, d); 8.46 (1H, dd); 9.04 (1H, s); 11.13 (1H, br s); ^{m/z} (LCMS; ESI+) 479 (MH⁺).

The requisite starting material was prepared as follows:

10 Preparation of 3,5-bis(benzyloxy)-N-(5-cyanopyridin-2-yl)benzamide

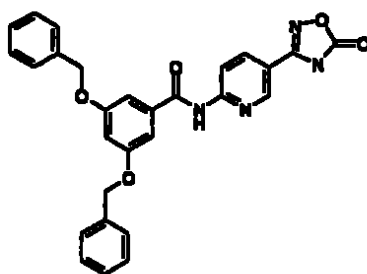


The title compound was prepared as described in Example A (route 1), starting from 2-amino-5-cyanopyridine and 3,5-bis(benzyloxy) benzoyl chloride, ¹H NMR δ (d₆-DMSO): 5.19 (4H, s); 6.89 (1H, m); 7.26-7.46 (12H, m); 8.27 (1H, dd); 8.33 (1H, d); 8.84 (1H, s); 11.23 (1H, br s); ^{m/z} (LCMS; ESI+) 436 (MH⁺).

The requisite 2-amino-5-cyanopyridine starting material may be purchased (Bionet Research, and other suppliers), or may be prepared according to the method given in WO95/06034.

20 EXAMPLE R

Route 17: 3,5-bis(benzyloxy)-N-[5-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)pyridin-2-yl]benzamide

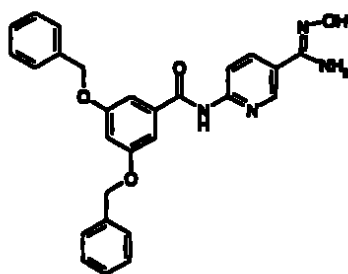


Ethyl chloroformate (32 μ L, 0.33 mmol) was added to a solution of 3,5-bis(benzyloxy)-*N*-(5-[(hydroxyamino)(imino)methyl]pyridin-2-yl)benzamide (140 mg, 0.30 mmol) in pyridine (5 mL). This solution was heated at reflux overnight. The mixture was cooled and concentrated under reduced pressure. DCM and methanol were used to dissolve the remaining material and the solution was washed with water. The organic solution was concentrated under reduced pressure and the residue was purified on silica by MPLC (eluting firstly with 5% methanol / DCM then 10% methanol / DCM). The title compound was obtained as a colourless solid (103 mg, 70%). ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 6.87 (1H, s); 7.28-7.46 (12H, m); 8.21 (1H, dd); 8.38 (1H, d); 8.79 (1H, s); 11.14 (1H, br s); m/z (LCMS; ESI+) 495 (MH^+).

10

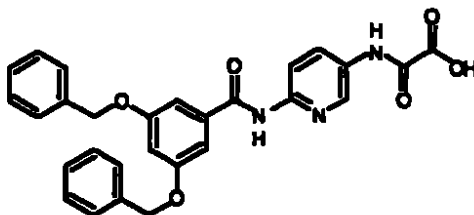
The requisite starting material was prepared as follows:

Preparation of 3,5-bis(benzyloxy)-*N*-(5-[(hydroxyamino)(imino)methyl]pyridin-2-yl)benzamide



15 A mixture of 3,5-bis(benzyloxy)-*N*-(5-cyanopyridin-2-yl)benzamide (212 mg, 0.49 mmol), triethylamine (170 μ L, 1.22 mmol) and hydroxylamine hydrochloride (85 mg, 1.22 mmol) in ethanol (5 mL) was heated at reflux overnight. The mixture was cooled and concentrated under reduced pressure. The residue was purified by MPLC on silica eluting with 5% methanol / DCM then 15% methanol / DCM. The title compound was obtained as a colourless solid (171 mg, 75%). ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 5.92 (2H, s); 6.87 (1H, s); 7.28-7.48 (12H, m); 8.06 (1H, dd); 8.17 (1H, d); 8.65 (1H, s); 9.68 (1H, s); 10.85 (1H, br s); m/z (LCMS; ESI+) 469 (MH^+).

25 The requisite 3,5-bis(benzyloxy)-*N*-(5-cyanopyridin-2-yl)benzamide was prepared as described in Example P (route 15).

39
Q**EXAMPLES****Route 18: [(2-{[3,5-bis(benzyloxy)benzoyl]amino}pyridin-5-yl)amino](oxo)acetic acid**

Methyl oxalyl chloride (37 μ L, 0.4 mmol) was added to a mixture of *N*-(5-aminopyridin-2-yl)-
5 3,5-bis(benzyloxy)benzamide (150 mg, 0.36 mmol) and triethylamine in DCM (5 mL). The
mixture was stirred for 1 hour under an atmosphere of nitrogen. The solution was diluted with
DCM and washed with water. The organics were concentrated under reduced pressure and the
residue was purified on silica by MPLC (eluting with 1% methanol / DCM to 15% methanol /
DCM) to give a colourless solid (110 mg). This material was dissolved in THF (2 mL). Water
10 (3 mL) and sodium hydroxide (0.5 mL, 2M, 1 mmol) were added. The mixture was stirred for
1 hour before being acidified with hydrochloric acid (2M) and diluted with water. The
resulting precipitate was isolated by filtration, washed with water and dried *in vacuo*. The title
compound was obtained as a colourless solid (88 mg, 50%). ^1H NMR δ (d_6 -DMSO): 5.18 (4H,
s); 6.88 (1H, s); 7.30-7.50 (12H, m); 8.17 (2H, s); 8.79 (1H, s); 10.79 (1H, s); 10.93 (1H, br
15 s); m/z (LCMS; ESI+) 498 (MH^+).

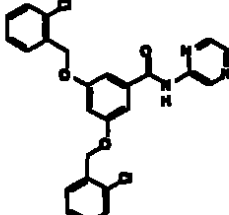
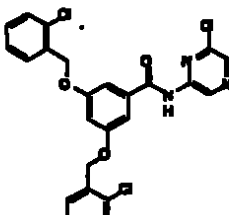
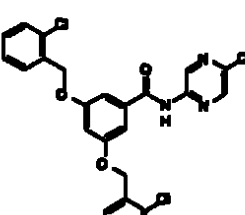
The requisite starting material was prepared according to Example H (route 7).

EXAMPLE T:

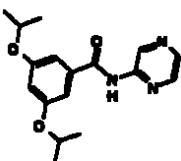
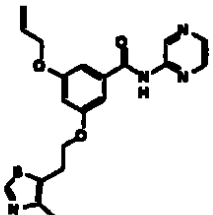
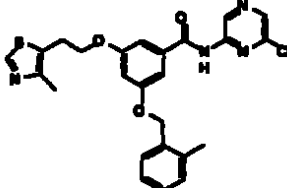
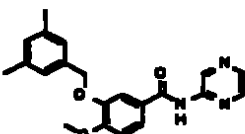
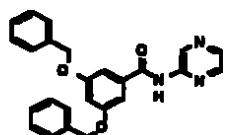
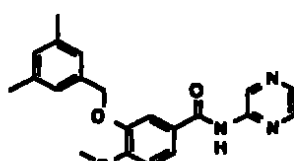
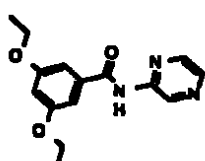
20 By analogous methods to those described above the following compounds, Example numbers
 T_1 to T_{20} , were also made.

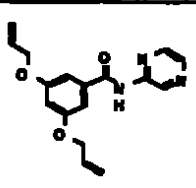
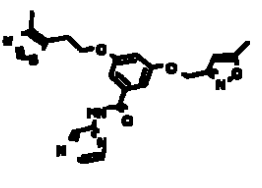
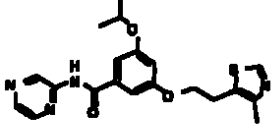
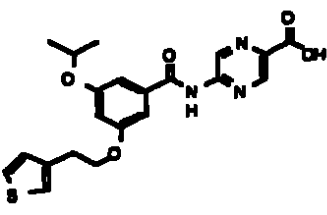
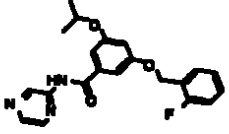
Compound T_9 was prepared by Route 1b (multi-parallel synthesis), as follows. To the
appropriate acid (6.0 mmol) in dichloromethane (25 mls) was added 1 drop of
25 dimethylformamide and the mixture stirred at room temperature under argon. The oxalyl
chloride (0.867 mls) was added to the acid and stirred at room temperature for 2 hrs. The
solvent was removed in Genevac DD4, and resulting residue azeotroped with
dichloromethane (3 x 10 mls), then dried high vacuum for 2hrs. The resulting acid chloride
was then dissolved in THF (30 mls) and 5mls of the solution was added to one of the set of

- six amines in THF / Pyridine (5mls). The resulting mixture was stirred overnight at room temperature, diluted with ethyl acetate (5mls). The resulting solution was transferred to the Alex automated extractor and washed with water (2x5mls), sodium hydrogen carbonate (5mls), 1M citric acid (5mls), brine (5mls) dried (magnesium sulphate) and evaporated in 5 Genevac DD4. The resulting gum was triturated with methanol (1-2 mls) and the resulting solid filtered, washed methanol and air-dried.

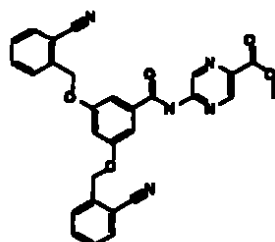
Example	Structure	Yield (%)	Purity (%)	1H NMR
1		1		1H NMR d (d6-DMSO): 5.26 (4H, s); 6.96 (1H, m); 7.38-7.45 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 8.43 (1H, d); 8.49 (1H, m); 9.42 (1H, m); 11.13 (1H, s).
2		1		1H NMR d (d6-DMSO): 5.25 (4H, s); 6.97 (1H, m); 7.38-7.45 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 8.64 (1H, d); 9.26 (1H, d); 11.33 (1H, s).
3		1		1H NMR d (d6-DMSO): 5.24 (4H, s); 6.95 (1H, s); 7.35-7.40 (6H, m); 7.50 (2H, m); 7.60 (2H, m); 8.61 (1H, s); 9.22 (1H, s); 11.25 (1H, br s).

Ex. No.	Structure	Route	NMR
4		1	¹ H NMR d (d6-DMSO): 5.36 (4H, s); 7.00 (1H, m); 7.44 (2H, d); 7.55-7.64 (2H, m); 7.77 (4H, m); 7.93 (2H, d); 8.43 (1H, d); 8.49 (1H, m); 9.43 (1H, s); 11.17 (1H, s).
5		1	¹ H NMR d (d6-DMSO): 3.90 (3H, s); 5.24 (4H, s); 6.97 (1H, m); 7.39 (6H, m); 7.50 (2H, m); 7.60 (2H, m); 9.02 (1H, s); 9.52 (1H, s); 11.54 (1H, br s).
6		2	¹ H NMR d (d6-DMSO): 5.24 (4H, s); 6.96 (1H, m); 7.39 (6H, m); 7.51 (2H, m); 7.62 (2H, m); 8.98 (1H, s); 9.48 (1H, s); 11.44 (1H, br s).
7		2 *	¹ H NMR d (d6-DMSO): 5.34 (4H, s); 7.00 (1H, s); 7.57 (2H, m); 7.75 (4H, m); 7.91 (2H, d); 9.00 (1H, s); 9.52 (1H, s); 11.53 (1H, s); 13.43, (1H br s).
8		1	¹ H NMR d (d6-DMSO): 2.29 (3H, s); 2.33 (3H, s); 3.24 (m, 2H); 4.21 (2H, t); 5.12 (2H, s); 6.80 (1H, m); 7.21 (4H, m); 7.31 (1H, m); 7.40 (2H, m); 8.39 (1H, m); 8.45 (1H, m); 8.82 (1H, s); 9.38 (1H, s); 11.06 (1H, br s).

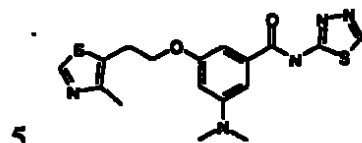
Example	Structure	Route	Mass	NMR
9		1b		¹ H NMR δ (d ₆ -DMSO): 1.25 (d, 12H), 4.7 (hept, 2H), 6.6 (d, 1H), 7.2 (d, 2H), 8.4 (d, 1H), 8.45 (t, 1H), 9.4 (s, 1H), 11.0 (br s, 1H).
10		1		¹ H NMR δ (d ₆ -DMSO): 2.37 (s, 3H), 3.24 (t, 2H), 4.23 (t, 2H), 4.65 (d, 2H), 5.28 (d, 1H), 5.42 (d, 1H), 6.05 (m, 1H), 6.75 (s, 1H), 7.23 (s, 2H), 8.43 (s, 1H), 8.84 (s, 1H), 9.40 (s, 1H), 11.07 (br s, 1H).
11		1		¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.35 (s, 3H), 3.21 (t, 2H), 4.21 (t, 2H), 5.13 (s, 2H), 6.81 (s, 1H), 7.14-7.26 (m, 4H), 7.32 (1H, s), 7.41 (1H, d), 8.51 (s, 1H), 8.81 (s, 1H), 9.39 (s, 1H), 11.34 (brs, 1H).
12		1	364	¹ H NMR δ (d ₆ -DMSO): 2.12 (s, 6H), 3.81 (s, 3H), 5.05 (s, 2H), 6.95 (s, 1H), 7.05 (s, 2H), 7.1 (s, 1H), 7.72 (d, 1H), 7.78 (s, 1H), 8.36 (d, 1H), 8.43 (s, 1H), 9.4 (s, 1H), 10.92 (br s, 1H)
13		1b	412	410
14		1b	330	
15		1b	288	

Example	Structure	Formula	Mass	NMR
16		1b	312	
17		1b	452	
18		1b	400	
19		2a, 1c	428	426 δ_H (500MHz, DMSO- d_6) 1.28 (6H, d), 3.07 (2H, t), 4.26 (2H, t), 4.70 (1H, m), 6.71 (1H, m), 7.12 (1H, m), 7.24 (2H, m), 7.30 (1H, m), 7.46 (1H, m), 8.98 (1H, d), 9.48 (1H, d), 11.33 (1H, s), 13.24 (1H, br s).
20		1a	382	

* For Example 7, the ester intermediate was prepared by route 1:



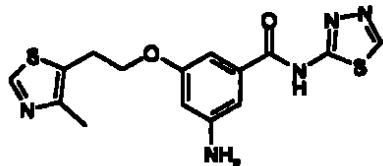
^1H NMR δ (d_6 -DMSO): 3.90 (3H, s); 5.34 (4H, s); 7.01 (1H, s); 7.43 (2H, s); 7.58 (2H, m);
5 7.74 (4H, m); 7.91 (2H, d); 9.02 (1H, s); 9.52 (1H, s); 11.57 (1H, br s).

EXAMPLE U**2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-dimethylamino] benzoylamino]-[1,3,4]-thiadiazole****(Route 19)**

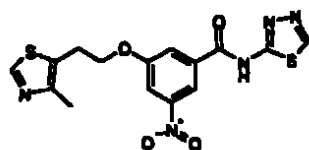
Formaldehyde (37% in water) (0.033ml, 0.44mM) was added to 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-amino] benzoylamino]-[1,3,4]-thiadiazole (27mg 0.074mM) and 4A molecular sieves (0.2g) in methanol (4ml)/acetonitrile (3ml)/ g.AcOH (2 drops) under an inert atmosphere at room temperature. After 150 mins sodium cyanoborohydride (7mg, 0.12mM) was added and the reaction mixture stirred for 40 hrs. The reaction mixture was filtered, concentrated *in vacuo*, the residue acidified with 2M HCl to precipitate a colourless solid. Purified on silica gel (50 to 75% EtOAc/iso-hexane) gave the title compound as a colourless solid (25mg, 85%); ¹H NMR δ (d₆-DMSO): 2.35 (s, 3H), 2.93 (s, 6H), 3.22 (m, 2H), 4.19 (m, 2H), 6.41 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 8.80 (s, 1H), 9.17 (s, 1H).

15

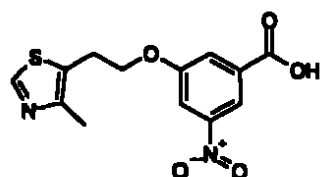
The requisite 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-amino] benzoylamino]-[1,3,4]-thiadiazole starting material was prepared as follows:



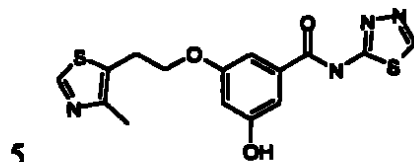
10% Palladium on carbon (80mg) was added under an argon atmosphere to a solution of 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-nitro] benzoylamino]-[1,3,4]-thiadiazole (0.38g, 0.99 mM) in ethyl acetate (40ml). Hydrogen gas was introduced and the reaction mixture stirred vigorously for 18hrs before filtering through celite, concentration *in vacuo* and replacement of the catalyst (80mg). After stirring under hydrogen gas for a further 18hrs a final catalyst change was carried out. After which the crude aniline was purified on silica gel (1% to 4% MeOH/DCM) to give 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-amino] benzoylamino]-[1,3,4]-thiadiazole as a colourless solid (0.1g, 28%); MS (M-H⁺)⁻ 360.



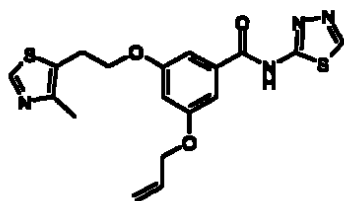
Oxalyl chloride (0.20ml, 2.35mM) was added to 3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-nitro benzoic acid (0.72g, 2mM) in dichloromethane (30ml) containing DMF (2 drops) under an argon atmosphere at room temperature. After 3hrs the reaction mixture was concentrated *in vacuo* and azeotroped with toluene to give an off-white solid. The acid chloride and 2-amino-[1,3,4]-thiadiazole (0.19g, 1.9 mM) were dissolved in DCM (20ml) then DIPEA (0.96ml, 5.6 mM) and DMAP (0.04g, 0.3 mM) added. After stirring overnight under argon the reaction mixture was concentrated, purified on silica gel (50%to75%to100% EtOAc/iso-hexane) gave a pale yellow solid which was triturated with MeOH to give 2-[3-(2-(4-methyl thiazol-5-yl) ethoxy)-5-nitro] benzoylamino]-[1,3,4]-thiadiazole as a colourless solid (0.30g, 48%); ¹H NMR δ (d₆-DMSO): 2.37 (s, 3H), 3.26 (t, 2H), 4.35 (t, 2H), 7.89 (m, 1H), 8.09 (s, 1H), 8.47 (s, 1H), 8.81 (s, 1H), 9.24 (s, 1H).



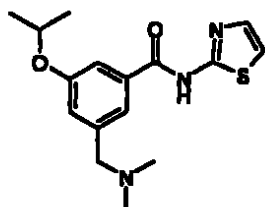
DIAD (3.16ml, 16.1mM) was added to a stirred solution of methyl 3-nitro-5-hydroxy benzoate (2.11g, 10.7mM), 4-(2-hydroxy ethyl)-5-methylthiazole (1.55ml, 12.8mM), and triphenylphosphine (4.21g, 16.1 mM) in THF (50ml) under an argon atmosphere at room temperature. After 1hr reaction mixture concentrated *in vacuo*, residue triturated with diethyl ether to give a colourless solid (triphenylphosphine oxide). Diethyl ether conc. to give a dark brown gum, purification on silica gel (50% to 75% EtOAc/iso-hexane) gave the product contaminated with reduced DIAD and triphenylphosphine oxide (6.8g). The crude product was dissolved/suspended in MeOH (80ml), 2M NaOH (20ml, 40 mM) added, heated at 65°C for 4 hrs then cooled and concentrated. The residue was diluted with water (140ml)/ 2M NaOH (40ml), the precipitated triphenylphosphine oxide filtered, then acidified with c. HCl to pH1-2. The precipitate was filtered, washed with water, dried under high-vacuum to give 3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-nitro benzoic acid as a colourless solid (3.12g, 79% over 2 steps); ¹H NMR δ (d₆-DMSO): 2.39 (s, 3H), 3.23 (t, 2H), 4.35 (t, 2H), 7.78 (s, 1H), 7.90 (m, 1H), 8.22 (s, 1H), 8.93 (s, 1H).

EXAMPLE V**2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-hydroxy] benzoylamino]-[1,3,4]-thiadiazole**
(Route 20)

A solution of 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-allyloxy] benzoylamino]-[1,3,4]-thiadiazole (1.1g, 2.7 mmol) in tetrahydrofuran (40ml) was stirred under an argon atmosphere and treated with Meldrum's acid (0.79g, 5.4mmol) and tetrakis (triphenyl phosphine) palladium (0) (825mg, 0.7mmol, 0.25 eq) and the resulting yellow solution stirred at ambient temperature for 2 hours. Sequential triturations with dichloromethane and hot tetrahydrofuran gave 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-hydroxy] benzoylamino]-[1,3,4]-thiadiazole as a colourless solid (0.59g, 59%), ¹H NMR δ (d₆-DMSO): 2.35 (s, 3H), 3.2 (t, 2H), 4.2 (t, 2H), 6.55 (m, 1H), 7.05 (s, 1H), 7.2 (s, 1H), 8.81 (s, 1H), 9.2 (s, 1H), 9.8 (br s, 1H); m/z 363 (M+H)⁺, 361 (M-H)⁻.



The requisite 2-[3-{2-(4-methyl thiazol-5-yl) ethoxy}-5-allyloxy] benzoylamino]-[1,3,4]-thiadiazole starting material was prepared according to the appropriate generic alkylation method, and the resulting benzoic acid coupled with 1,3,4-thiadiazole according to Route 1. The analytical data on all intermediates was consistent with the proposed structures.

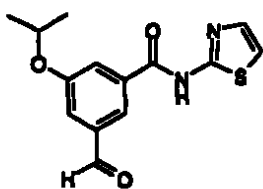
43
~~43~~**EXAMPLE W****2-(3-isopropoxy-5-dimethylaminomethyl)benzoyl aminothiazole****(Route 21)**

- 5 A solution of 2-(3-isopropoxy-5-formyl)benzoyl aminothiazole (0.11g, 0.39mmol) in dichloromethane was treated with dimethylamine (0.074ml of an approx. 5.6M solution in ethanol, 0.41mmol, 1.1 eq) and stirred under argon for 10 mins. To the solution was added sodium tris-acetoxy borohydride (0.11g, 0.53mmol, 1.4 eq), and the resulting mixture stirred overnight at ambient temperature. Further reagents were then added (same quantities as
- 10 before) and the mixture again stirred overnight at ambient temperature. The solution was treated with saturated sodium bicarbonate solution (10ml) and stirred for 20 mins; it was then extracted twice with dichloromethane, the organic extracts dried over magnesium sulfate and evaporated *in vacuo* to give the product as a colourless oil. This was dissolved in ethyl acetate and the solution treated with an ethereal solution of HCl (excess of 1M); the precipitate thus
- 15 formed was filtered under argon and washed with diethyl ether to give 2-(3-isopropoxy-5-dimethylaminomethyl)benzoyl aminothiazole hydrochloride as a colourless solid (0.1g, 72%).
¹H NMR δ (d_6 -DMSO): 1.31 (d, 6H), 2.71 (s, 6H), 4.26 (m, 2H), 4.76 (m, 1H), 7.29 (d, 1H), 7.42 (m, 1H), 7.55 (d, 1H), 7.70 (s, 1H), 10.66 (bs, 1H).

- 20 The requisite starting material was prepared as follows:

EXAMPLE X**2-(3-isopropoxy-5-formyl)benzoyl aminothiazole****(Route 22):**

25



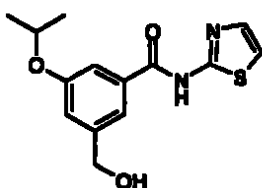
A solution of 2-(3-isopropoxy-5-hydroxymethyl)benzoyl aminothiazole (0.115g, 0.39mmol) in tetrahydrofuran (8ml) was treated with manganese dioxide (0.27g, 3.1mmol, 8eq) and the resulting suspension stirred overnight at ambient temperature; additional oxidant (0.1g portions) was added until all the starting material was consumed (tlc). The suspension was
 5 filtered, the residue washed well with ethyl acetate, and the combined filtrate and washings evaporated *in vacuo* to give the product as a pale yellow solid, ¹H NMR δ (d₆-DMSO): 1.31 (d, 6H), 4.82 (m, 1H), 7.26 (d, 1H), 7.56 (d, 1H), 7.59 (s, 1H), 7.94 (d, 1H), 8.15 (s, 1H), 10.00 (s, 1H), 12.77 (bs, 1H).

10 The requisite starting material was prepared as follows:

EXAMPLE Y

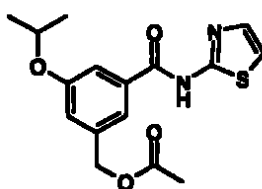
2-(3-isopropoxy-5-hydroxymethyl)benzoyl aminothiazole

(Route 23)



15

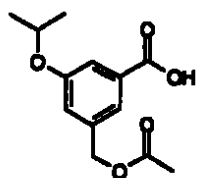
Standard ester cleavage of 2-(3-isopropoxy-5-acetoxymethyl)benzoyl aminothiazole (0.15g, 0.46 mM) using 2M NaOH/THF/MeOH for 1 hour gave 2-(3-isopropoxy-5-hydroxymethyl)benzoyl aminothiazole as a colourless solid (0.149g, 100%); ¹H NMR δ (d₆-DMSO): 1.28 (d, 6H), 4.51 (s, 2H), 4.71 (m, 1H), 7.05 (s, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 7.53
 20 (d, 1H), 7.58 (s, 1H), 12.50 (bs, 1H).



The requisite 2-(3-isopropoxy-5-acetoxymethyl)benzoyl aminothiazole was prepared by a standard coupling between 3-isopropoxy-5-acetoxymethyl benzoyl chloride and 2-
 25 aminothiazole according to Route 1, to give the title compound as a pale yellow oil, δ (d₆-DMSO): 1.3 (d, 6H), 2.1 (s, 3H), 4.75 (hept, 1H), 5.1 (s, 2H), 7.15 (s, 1H), 7.25 (d, 1H), 7.65 (d, 1H), 7.6 (m, 2H), 12.6 (bs, 1H).

44
X

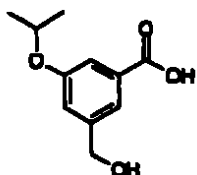
The requisite 3-isopropoxy-5-acetoxymethyl benzoic acid was prepared as follows:



A solution of 3-isopropoxy-5-hydroxymethyl benzoic acid (0.77g, 3.7mmol) in
5 dichloromethane (20ml) was cooled (ice-bath) and stirred under argon; pyridine (1.18ml, 14.6mmol, 4eq) was added followed dropwise by acetyl chloride (0.55ml, 7.7 mmol, 2.1 eq). The mixture was stirred for 5 mins, then allowed to warm to ambient temperature over 90 mins. Water (20ml) was added, the mixture stirred for 2 hrs, then allowed to stand overnight. The organic layer was separated, the aqueous portion washed with dichloromethane, and the
10 dichloromethane fractions combined and evaporated. The resulting pale yellow oil was dissolved in ethyl acetate and the solution washed with 0.05M aqueous HCl (20ml); the organic layer was separated, dried over magnesium sulfate and evaporated *in vacuo* to give the product as a pale yellow solid, ¹H NMR δ (d₆-DMSO): 1.25 (d, 6H), 2.06 (s, 3H), 4.65 (hept, 1H), 5.05 (s, 2H), 7.12 (s, 1H), 7.31 (d, 1H), 7.46 (s, 1H).

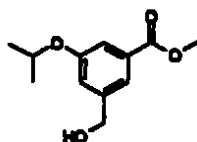
15

The requisite 3-isopropoxy-5-hydroxymethyl benzoic acid starting material was prepared as follows:



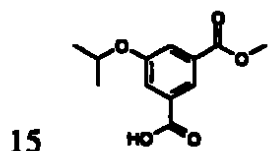
Standard 2M NaOH/THF/MeOH cleavage of methyl 3-isopropoxy-5-hydroxymethyl benzoate
20 (1.12g, 5.0 mM) gave the title compound as a colourless solid (0.98g, 94%); ¹H NMR δ (d₆-DMSO): 1.25 (d, 6H), 4.47 (s, 2H), 4.60 (m, 1H), 5.23 (bs, 1H), 7.06 (s, 1H), 7.24 (s, 1H), 7.45 (s, 1H).

The requisite methyl 3-isopropoxy-5-hydroxymethyl benzoate starting material was prepared
25 as follows:



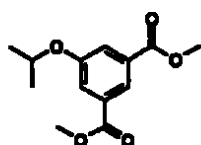
Mono-methyl-5-isopropoxy-isophthalate (5.15g, 21.6 mM) was dissolved in THF (180ml), cooled to 2°C and borane:THF complex (72ml of 1.5M solution in THF, 0.11 mM) added dropwise over 15 mins, maintaining an internal temperature of < 5°C. After 15 mins the reaction mixture was warmed to ambient temperature, stirred for 3 hrs before cooling (ice bath) and quenching with pieces of ice. When no further reaction observed brine (150ml)/ diethyl ether (150ml) added. The organic layer was removed, aqueous extracted with additional diethyl ether (1x100ml), combined organics washed with brine (1x100ml), dried (MgSO₄), filtered and concentrated. Purified on silica gel (20-25% EtOAc/isohexane) to give the title compound as a colourless solid (3.57g, 74%); ¹H NMR δ (d₆-DMSO): 1.26 (d, 6H), 3.82 (s, 3H), 4.50 (d, 2H), 4.63 (m, 1H), 5.26 (t, 1H (-OH)), 7.10 (s, 1H), 7.25 (s, 1H), 7.47 (s, 1H).

The requisite mono-methyl-5-isopropoxy-isophthalate starting material was prepared as follows:



2M NaOH (1.03g, 25.9 mM) in methanol (9 ml) was added to a solution of dimethyl-5-isopropoxy-isophthalate (5.68g, 22.5 mM) in acetone (45ml) and stirred at ambient temperature overnight. The reaction mixture was concentrated, acidified (2M HCl) to pH1-2, filtered, washed with water and dried under high vacuum to give 14279/66/1 as a colourless solid (5.25g, 98%) (contains 15-20% diacid); MS (M-H)⁺ 237.

The requisite dimethyl-5-isopropoxy-isophthalate starting material was prepared as follows:



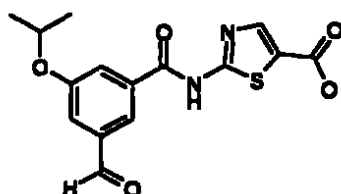
Dimethyl-5-hydroxy-isophthalate (5.2g, 24.6 mM), potassium carbonate (4.07g, 29.5 mM), potassium iodide (0.82g, 4.9 mM) and 2-bromopropane (2.4ml, 25.8 mM) in DMF (50ml) was heated at 90°C for 3hrs, after which additional 2-bromopropane (2.4ml), potassium carbonate (2.2g) was added, heated for a further 4hrs then cooled to room temperature and concentrated. EtOAc (150ml) was added then washed with water, brine, dried (MgSO₄),

filtered and concentrated to give a pale yellow oil which solidified on standing (6.0g, 97%); MS (MH⁺) 253.

EXAMPLE Z

5 2-(3-isopropoxy-5-formyl)benzoyl aminothiazole-5-carboxylic acid

(Route 24)



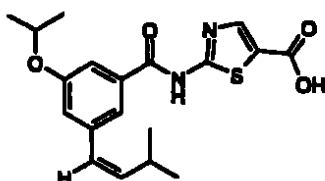
A solution of 2-(3-isopropoxy-5-hydroxymethyl)benzoyl aminothiazole-5-carboxylic acid (0.42g, 1.25mmol) in tetrahydrofuran (50ml) was treated with Dess-Martin periodinane (DMP, 0.58g, 1.37mmol, 1.1 eq) and stirred at ambient temperature for 90 mins. The solvent was removed *in vacuo*, and the residue treated with dichloromethane and filtered. The residue was partitioned between ethyl acetate and sat'd sodium bicarbonate solution containing sodium thiosulfate solution (ca 7 eq of 2.1 M), and the resulting 2-phase mixture stirred vigorously before being acidified to ca pH6. The title compound was isolated by filtration as a colourless solid, (0.145g, 35%), ¹H NMR δ (d₆-DMSO): 1.32 (d, 6H), 4.79 (m, 1H), 7.62 (m, 1H), 7.92 (m, 1H), 8.13 (s, 1H), 8.18 (s, 1H), 10.03 (s, 1H).

The requisite 2-(3-isopropoxy-5-hydroxymethyl)benzoyl aminothiazole-5-carboxylic acid starting material was prepared according to the procedure given in Route 2a and is exemplified as Example II_{g1}.

EXAMPLE AA

Z-{2-[3-isopropoxy-5-(3-methyl-but-1-enyl)]benzoyl aminothiazole-5-carboxylic acid}

(Route 25)



A solution of iso-butyl triphenyl phosphonium bromide (0.45g, 1.13mmol, 3.1 eq) in tetrahydrofuran (20ml) was treated with potassium t-butoxide (1.1ml of 1M in

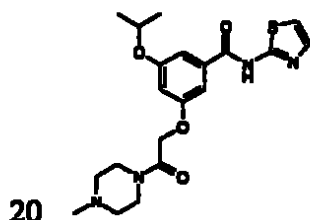
tetrahydrofuran, 1.13mmol, 3.1 eq) and stirred at 0 deg C under argon. To this was added 2-(3-isopropoxy-5-formyl)benzoyl aminothiazole-5-carboxylic acid (0.122g, 0.36mmol), and the resulting solution stirred for 100 mins, allowing to warm to ambient temperature. Water was added and the solvent removed *in vacuo*; the residue was partitioned between water and ethyl acetate and the layers separated. The aqueous portion was neutralised (2M HCl) and extracted twice with ethyl acetate; the organic extracts were dried (MgSO₄), filtered and concentrated and the residue purified by chromatography on silica gel (10g Bondelut cartridge, eluting with dichloromethane containing methanol, 10% v/v) to give the title compound as a colourless solid (0.012g, 9%); ¹H NMR δ (d₆-DMSO): 1.01 (d, 6H), 1.29 (d, 6H), 2.81 (m, 1H), 4.72 (m, 1H), 6.53 (dd, 1H), 6.29 (d, 1H), 6.97 (s, 1H), 7.50 (s, 1H), 7.53 (s, 1H), 8.11 (s, 1H), 8.18 (s, 1H).

The requisite 2-(3-isopropoxy-5-formyl)benzoyl aminothiazole-5-carboxylic acid was prepared according to the procedure given under Example Z (Route 24); see Example II₉₉.

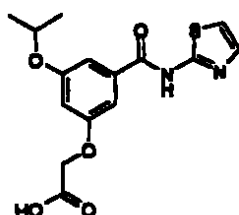
EXAMPLE BB

2-[3-isopropoxy-5-(4-methyl-1-piperidinocarbonylmethylenoxy)] benzoyl aminothiazole.

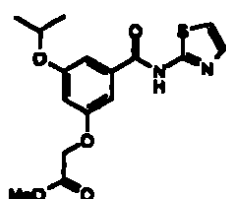
(Route 26)



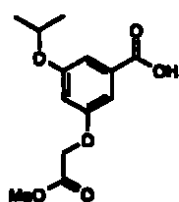
This was prepared by a standard acid chloride coupling (Example A, Route 1), starting from 2-(3-isopropoxy-5-carboxymethylene oxy) benzoyl aminothiazole, to give the title compound, ¹H NMR δ (d₆-DMSO): 1.28 (d, 6H), 2.18 (s, 3H), 2.24 (m, 2H), 2.32 (m, 2H), 3.44 (ap t, 4H), 4.65 (m, 1H), 4.85 (s, 2H), 6.68 (ap t, 1H), 7.19 (m, 1H), 7.24 (ap d, 2H), 7.55 (ap d, 1H), 12.45 (bs, 1H); m/z 419 (M+H)⁺, 417 (M-H)⁻.

46
X
X

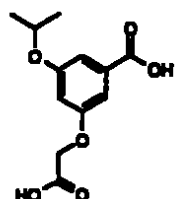
The requisite 2-(3-isopropoxy-5-carboxymethylene oxy) benzoyl aminothiazole was prepared from 2-(3-isopropoxy-5-methoxycarbonylmethylene oxy) benzoyl aminothiazole by standard ester hydrolysis (Route 2a); ^1H NMR δ (d_6 -DMSO): 1.28 (d, 6H), 4.69 (m, 1H), 4.73 (s, 2H), 6.66 (ap t, 1H), 7.22 (s, 1H), 7.27 (ap d, 2H), 7.53 (ap d, 1H); m/z 337.31 ($M+H$) $^+$ 335.27 ($M-H$) $^-$



The requisite 2-(3-isopropoxy-5-methoxycarbonylmethylene oxy) benzoyl aminothiazole starting material was prepared from 3-isopropoxy-5-(methoxycarbonyl)methoxybenzoic acid and 2-aminothiazole (48% isolated yield) by a standard acid chloride coupling (Route 1); ^1H NMR δ (d_6 -DMSO): 1.27 (d, 6H), 3.70 (s, 3H), 4.71 (m, 1H), 4.86 (s, 2H), 6.99 (t, 1H), 7.23 (t, 1H), 7.26-7.27 (m, 2H), 12.53 (s, 1H); m/z 351.31 ($M+H$) $^+$, 349.28 ($M-H$) $^-$

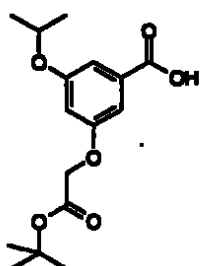


The requisite starting material was prepared from 3-isopropoxy-5-(methoxycarbonyl methylene oxy) benzoic acid was prepared by monoesterification of 3-isopropoxy-5-(carboxymethylene oxy) benzoic acid (78% isolated yield) using the conditions of Ram and Charles, *Tetrahedron* 1997, 53 (21), pp.7335-7340: ^1H NMR δ (d_6 -DMSO): 1.25 (d, 6H), 3.69 (s, 3H), 4.65 (m, 1H), 4.83 (s, 2H), 6.71 (ap t, 1H), 6.98 (s, 1H), 7.01 (s, 1H), 12.97 (bs, 1H); m/z 554.27 ($2M+NH_4$) $^+$, 267.26 ($M-H$) $^-$

3-isopropoxy-5-(carboxymethoxy)benzoic acid

The title compound was prepared from methyl (3-isopropoxy-5-(t-butylloxycarbonyl)methoxy)benzoate (56% isolated yield) using standard hydrolysis method

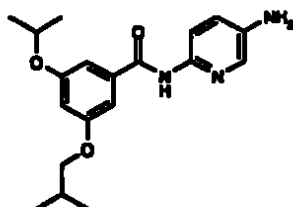
5 2a. ^1H NMR δ (d_6 -DMSO): 1.25 (d, 6H), 4.62 (m, 1H), 4.69 (s, 2H), 6.67 (ap t, 1H), 6.96 (s, 1H), 7.02 (s, 1H), 12.95 (bs, 1H); m/z 253.27 (M-H) $^+$



The requisite methyl (3-isopropoxy-5-(t-butylloxycarbonyl)methoxy)benzoate was prepared
10 according to generic Alkylation Method B. The analytical data on all intermediates was consistent with the proposed structures.

EXAMPLE CC**3-amino-6-(3-isobutoxy-5-isopropoxy benzoyl) aminopyridine**

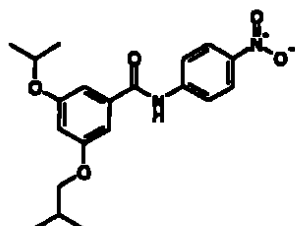
15 **(Route 7b)**



To a solution of 2-(3-isobutoxy-5-isopropoxybenzoyl)amino-5-nitropyridine (1.74g, 4.66mmol) in ethanol (20ml) was added 10% Pd/C under an inert atmosphere. The reaction
20 mixture was placed under a hydrogen atmosphere and stirred vigorously for 16h. The reaction mixture was flooded with argon, and then diluted with water (20ml) and acidified with 2M HCl (5ml). The suspension was filtered through celite, and the filtrate evaporated *in vacuo*.

The residue was partitioned between ethyl acetate (25ml) and saturated sodium bicarbonate (25ml), and the organic extract dried over MgSO_4 . Evaporation *in vacuo* afforded the title compound as a brown solid (1.30g, 81%).

^1H NMR δ (d_6 -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.00 (m, 1H), 3.78 (d, 2H), 4.69 (m, 1H), 5.12 (s, 2H), 6.58 (t, 1H), 6.99 (dd, 1H), 7.1 (ap d, 2H), 7.73-7.78 (m, 2H), 10.24 (bs, 1H); m/z 344.41 ($\text{M}+\text{H}$) $^+$

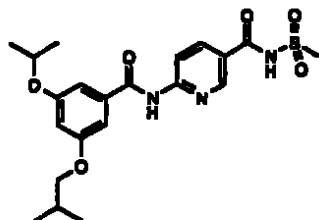


- 10 The requisite 2-(3-isobutyloxy-5-isopropoxy) benzoyl amino-5-nitropyridine was prepared according to Route 1 (see Example 10 in Pyridine table); ^1H NMR δ (d_6 -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 2.01 (m, 1H), 3.60 (d, 2H), 4.71 (m, 1H), 6.67 (ap t, 1H), 7.17 (ap d, 2H), 8.39 (d, 1H), 8.63 (dd, 1H), 9.20 (d, 1H), 11.43 (bs, 1H); m/z 374 ($\text{M}+\text{H}$) $^+$, 372 ($\text{M}-\text{H}$) $^-$.

15 EXAMPLE DD

2-[(3-isobutyloxy-5-isopropoxy) benzoyl] amino -5-(N-methylsulfonyl)-carboxamido pyridine

(Route 27)



- 20 2-[(3-isobutyloxy-5-isopropoxy) benzoyl] aminopyridine-5-carboxylic acid (95mg, 0.255mmol) was stirred with EDC (59mg, 0.306mmol), DMAP (37mg, 0.306mmol) and methanesulfonamide (36mg, 0.378mmol) in DCM (3ml) under an inert atmosphere for 16h. The reaction mixture was diluted with further DCM (10ml) and extracted with water (2x5ml). 1M citric acid (5ml) and brine (5ml). Filtration through a PTFE membrane and evaporation *in vacuo* afforded the title compound as a colourless crystalline solid (90mg, 79%). ^1H NMR δ (d_6 -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.03 (m, 1H), 3.01 (s, 3H), 3.79 (d, 2H), 4.70 (m, 1H),
- 25

- 86 -

6.63 (ap t, 1H), 7.14 (ap d, 2H), 7.70 (dd, 1H), 8.12 (d, 1H), 8.34 (ap d, 1H), (9.83, s, 1H), 10.81 (bs, 1H);

m/z 422.37 (M+H)⁺, 420.30 (M-H)⁻

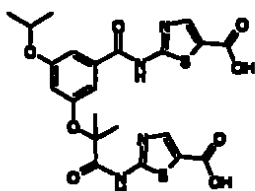
- 5 The requisite 2-[(3-isobutyloxy-5-isopropoxy) benzoyl] aminopyridine-5-carboxylic acid starting material was prepared from methyl 2-[(3-isobutyloxy-5-isopropoxy) benzoyl] aminopyridine-5-carboxylate by standard hydrolysis (Route 2a);

The requisite methyl 2-(3-isobutyloxy-5-isopropoxy) benzoyl aminopyridine-5-carboxylate
10 was prepared by standard acid chloride coupling (Route 1);

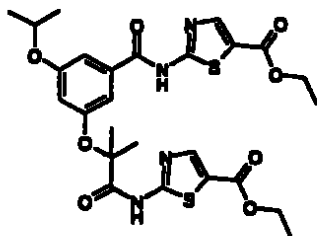
EXAMPLE EE

2-{[3-isopropoxy-5-[1-methyl-1-(5-carboxy-thiazol-2-yl) aminocarbonyl]] ethoxy benzoyl} aminothiazole-5-carboxylic acid

15 (Route 28)



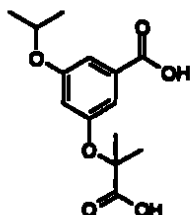
- Ethyl 2-{3-isopropoxy-5-[1-methyl-1-(5-ethoxycarbonyl-thiazol-2-yl) aminocarbonyl]] ethoxy benzoyl} aminothiazole-5-carboxylate was hydrolysed by a standard method according to Example B Route 2a to give 2-{3-isopropoxy-5-[1-methyl-1-(5-carboxy-thiazol-2-yl)
20 aminocarbonyl]] ethoxy benzoyl} aminothiazole-5-carboxylic acid, ¹H NMR δ (d₆-DMSO): 1.22 (d, 6H), 1.61 (s, 6H), 4.58-4.64 (m, 1H), 6.62 (s, 1H), 7.19 (s, 1H), 7.40 (s, 1H), 8.05 (s, 1H), 8.12 (s, 1H), m/z 533 (M-H)⁻.



25

The requisite ethyl 2-{3-isopropoxy-5-[1-methyl-1-(5-ethoxycarbonyl-thiazol-2-yl)aminocarbonyl]] ethoxy benzoyl} aminothiazole-5-carboxylate starting material was prepared by a standard acid chloride method according to Example A Route 1, starting from 3-isopropoxy-5-[(1-methyl-1-carboxy) ethoxy] benzoic acid.

5



The requisite 3-isopropoxy-5-[(1-methyl-1-carboxy) ethoxy] benzoic acid.

starting material was prepared according to the procedure described by Corey et al, JACS 91 p4782 (1969), starting from methyl 3-isopropoxy-5-hydroxy benzoate. The methyl ester

10 was hydrolysed under the reaction conditions, and the product was isolated by extraction into aqueous sodium bicarbonate solution followed by acidification and extraction into ethyl acetate. The organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude product as a pale yellow solid. Recrystallisation from hexane gave the title compound as a colourless solid; ¹H NMR δ (d₆-DMSO): 1.15 (d, 6H), 1.5 (s, 6H), 4.55 (hept, 1H), 6.55 (dd, 1H), 6.95 (m, 1H), 7.05 (m, 1H), 13.0 (br s, 1H); m/z 283 (M+H)⁺, 281 (M+H)⁻.

EXAMPLE FF:

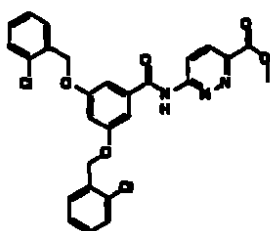
By analogous methods to those described above the following pyridazine compounds, Example numbers FF₁ to FF₃, were also made.

20

Example	Structure	Route	MW	mp (°C)	NMR (d ₆ -DMSO)
1		1			¹ H NMR δ (d ₆ -DMSO): 3.95 (3H, s); 5.25 (4H, s); 6.95 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.65 (2H, m); 8.25 (1H, d); 8.6 (1H, d); 11.85 (1H, br s).

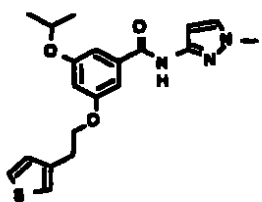
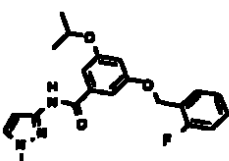
2		2	524/526	522	¹ H NMR d (d ₆ -DMSO): 2.0 (1H, s); 5.25 (4H, s); 6.95 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.25 (1H, d); 8.55 (1H, d); 11.8 (1H, br s). MS and NMR contained signals due to acid starting material (~20 mol%); NMR contained signals due to ethyl acetate, (~33 mol%)
3		1			¹ H NMR d (d ₆ -DMSO): 5.24 (4H, s); 6.93 (1H, m); 7.37 (6H, m); 7.50 (2H, m); 7.61 (2H, m); 7.71 (1H, dd); 8.36 (1H, d); 9.00 (1H, d).
4		2 *	524/526	522/524	¹ H NMR δ (d ₆ -DMSO): 5.2 (4H, s); 6.95 (1H, m); 7.15 (1H, s); 7.3 (1H, d); 7.4 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 9.1 (2H, s); 11.35 (1H, br s); the spectrum also contains signals due to acid starting material (~40 mol%)
5		2a, 1c (c)	428		δ _H (300MHz, DMSO-d ₆) 1.29 (6H, d), 3.08 (2H, t), 4.30 (2H, t), 4.74 (1H, m), 6.73 (1H, s), 7.13 (1H, m), 7.24 (1H, s), 7.27 (1H, s), 7.34 (1H, m), 7.52 (1H, m), 8.25 (1H, d), 8.56 (1H, d), 11.75 (1H, s), 13.66 (1H, br s).

* For Example 15, the ester intermediate was prepared by route 1 and is exemplified as Example 12:

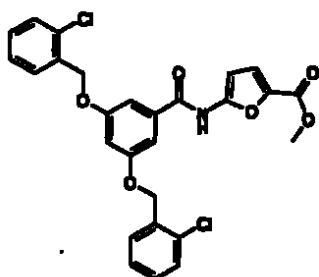
**EXAMPLE GG:**

- 5 By analogous methods to those described above the following compounds, Example numbers GG₁ to GG₇, were also made.

EXAMPLE	STRUCTURE	REF	1H-NMR	13C-NMR	ANAL
1		2 *			1H NMR d (d6-DMSO): 5.22 (4H, s); 6.54 (1H, d); 6.93 (1H, d); 7.27 (1H, d); 7.32-7.44 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 11.85 (1H, s); 12.86 (1H, br s).
2					1H NMR d (d6-DMSO): 3.75 (3H, s); 5.21 (4H, s); 6.55 (1H, d); 6.88 (1H, m); 7.31 (1H, m); 7.38 (4H, m); 7.38 (2H, m); 7.56 (1H, m); 7.59 (2H, m); 10.80 (1H, br s).
3		1a	331		
4		1a	332.53	330.51	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.36 (6H, d), 2.08 (1H, m), 2.30 (3H, s), 3.75 (d, 2H), 4.60 (1H, hept), 6.66 (2H, m), 7.08 (2H, m), 9.85 (1H, br s).
5		1a	376.47	374.45	δ_H (300MHz, DMSO-d ₆) 0.98 (6H, d), 1.27 (6H, d), 2.02 (1H, m), 3.80 (2H, d), 3.84 (3H, s), 4.68 (1H, hept), 6.62 (1H, s), 7.12 (3H, m), 10.95 (1H, br s), 13.65 (1H, br s).

Example	Structure	Route	MP (°C)	Yield (%)	NMR
6		1b (HA TU)	386.47		δ_H (300MHz, CDCl ₃) 1.35 (6H, d), 3.13 (2H, t), 3.72 (3H, s), 4.16 (2H, t), 4.53 (1H, hept), 6.60 (1H, s), 6.83 (1H, s), 7.00 (4H, m) 7.28 (2H, m), 8.98 (1H, br s).
7		1a	384		

* For GG₁, the ester intermediate was prepared by route 1:

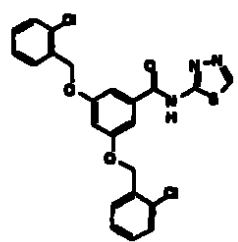


5 ¹H NMR δ (d₆-DMSO): 3.80 (3H, s); 5.23 (1H, m); 6.61 (1H, d); 6.95 (1H, s); 7.33-7.43 (7H, m); 7.50-7.55 (2H, m); 7.60-7.63 (2H, m); 11.90 (1H, br s).

EXAMPLE HH:

By analogous methods to those described above the following compounds, Example numbers

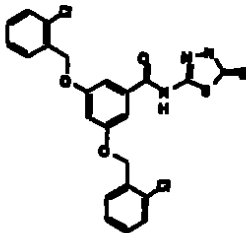
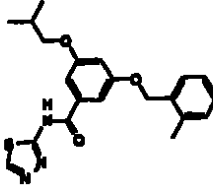
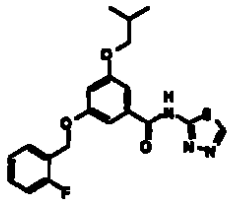
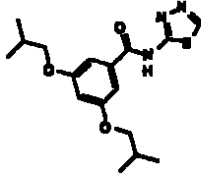
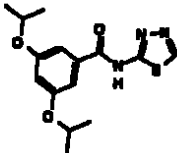
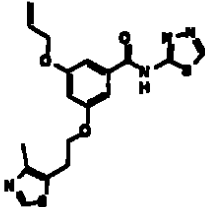
10 HH₁ to HH₃₃, were also made.

Example	Structure	Route	MP (°C)	Yield (%)	NMR
1		1	484		¹ H NMR d (d ₆ -DMSO): 5.26 (4H, s); 7.02 (1H, s); 7.40 (4H, m); 7.46 (2H, m); 7.54 (2H, m); 7.63 (2H, m); 9.24 (1H, s); 13.08 (1H, br s).

50

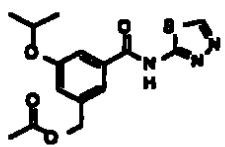
Example	Structure	Yield (%)	mp (°C)	1H NMR (d6-DMSO)
2		1		1H NMR d (d6-DMSO): 2.63 (3H, s); 5.24 (4H, s); 6.96 (1H, s); 7.35-7.45 (6H, m); 7.51 (2H, m); 7.61 (2H, m); 12.84 (1H, br s).
3		1		1H NMR d (d6-DMSO): 1.38 (3H, t), 3.25 (2H, q); 5.25 (4H, s); 6.97 (1H, s); 7.41 (6H, m); 7.54 (2H, m); 7.64 (2H, m); 13.13 (1H, br s).
4		1		1H NMR d (d6-DMSO): 1.32 (3H, t), 4.32 (2H, q); 5.20 (4H, s); 6.78 (1H, s); 7.39 (4H, m); 7.46 (2H, m); 7.53 (2H, m); 7.64 (2H, m).
5		1		1H NMR d (d6-DMSO): 4.20 (3H, s); 5.28 (4H, s); 6.98 (1H, s); 7.42 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 12.78 (1H, br s).
6		2	530, 532	1H NMR d (d6-DMSO): 5.24 (4H, s); 6.96 (1H, s); 7.37 (4H, m); 7.33 (2H, m); 7.53 (2H, m); 7.62 (2H, m).
7		1		1H NMR d (d6-DMSO): 5.25 (4H, s); 6.74 (1H, m); 6.99 (1H, s); 7.23 (1H, m); 7.41 (4H, m); 7.49 (2H, m); 7.53 (2H, m); 7.65 (2H, m); 7.97 (1H, s); 13.20 (1H, br s).

Ex. No.	Structure	Yield %	MP °C	IR (cm ⁻¹)	NMR
8		1			¹ H NMR d (d6-DMSO): 5.34 (4H, s); 7.03 (1H, s); 7.49 (2H, m); 7.57 (2H, m); 7.75 (4H, m); 7.91 (2H, d); 9.22 (1H, s); 13.06 (1H, br s).
9		19		564, 566	¹ H NMR d (d6-DMSO): 5.20 (4H, s); 6.68 (1H, m); 7.37 (4H, m); 7.45 (2H, m); 7.50 (2H, m); 7.62 (2H, m).
10		1	566	564, 566	¹ H NMR d (d6-DMSO): 5.22 (4H, s); 6.99 (1H, m); 7.39 (4H, m); 7.45 (2H, m); 7.51 (2H, m); 7.60 (2H, m); 13.34 (1H, br s).
11		1			¹ H NMR d (d6-DMSO): 2.33 (3H, s), 2.37 (3H, s); 3.25 (2H, m); 4.21 (2H, t); 5.14 (2H, s); 6.84 (1H, m); 7.22 (3H, m); 7.31 (1H, s); 7.40 (2H, m); 8.83 (1H, s); 9.21 (1H, s); 12.99 (1H, br s).
12		1			¹ H NMR d (d6-DMSO): 1.33 (3H, t); 2.32 (3H, s), 2.35 (3H, s); 3.22 (2H, m); 4.21 (2H, t); 4.40 (2H, q); 5.13 (2H, s); 6.87 (1H, m); 7.22 (3H, m); 7.33 (1H, m); 7.41 (2H, m); 8.82 (1H, s); 13.46 (1H, br s).

Example	Structure	Rate	M _r	M _r	NMR
13				516, 518	¹ H NMR δ (d ₆ -DMSO): 5.21 (4H, s); 6.98 (1H, m); 7.34-7.40 (6H, m); 7.50 (2H, m); 7.59 (2H, m).
14			398		¹ H NMR δ (d ₆ -DMSO): 1.0 (d, 6H), 2.0 (hept, 1H), 2.35 (s, 3H), 3.8 (d, 2H), 5.2 (s, 2H), 6.85 (d, 1H), 7.15-7.25 (m, 3H), 7.30 (d, 1H), 7.4 (2H, m), 9.2 (s, 1H), 11.6 (br s, 1H).
15			402		¹ H NMR δ (d ₆ -DMSO): 1.0 (d, 6H), 2.0 (hept, 1H), 3.8 (d, 2H), 5.2 (s, 2H), 6.85 (s, 1H), 7.2-7.3 (m, 2H), 7.35 (s, 1H), 7.4 (m, 2H), 7.6 (t, 1H), 9.2 (s, 1H), 13.0 (br s, 1H).
16			350		
17			322		¹ H NMR δ (d ₆ -DMSO): 1.3 (d, 12H), 4.7 (hept, 2H), 6.65 (s, 1H), 7.25 (s, 2H), 9.2 (s, 1H), 12.95 (br s, 1H).
18					¹ H NMR δ (d ₆ -DMSO): 2.34 (s, 3H), 3.23 (t, 2H), 4.21 (t, 2H), 4.62 (d, 2H), 5.26 (d, 1H), 5.40 (d, 1H), 6.05 (m, 1H), 6.75 (s, 1H), 7.31 (s, 2H), 8.83 (s, 1H), 9.20 (s, 1H), 12.48 (br s, 1H).

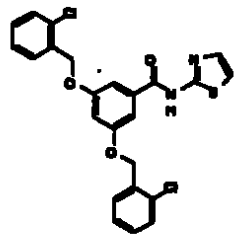
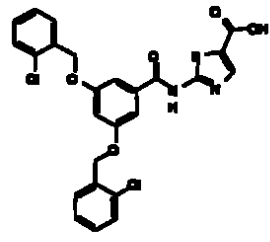
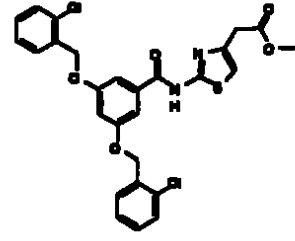
Example	Structure	Route	MP (°C)	λ_{max} (nm)	NMR
19					¹ H NMR δ (d ₆ -DMSO): 2.31 (s, 3H), 2.34 (s, 3H), 3.22 (t, 2H), 4.21 (t, 2H), 5.13 (s, 2H), 6.84 (s, 1H), 7.15-7.25 (m, 3H), 7.26 (1H, m), 7.39 (2H, m), 8.81 (s, 1H).
20					¹ H NMR δ (d ₆ -DMSO): 2.37 (s, 3H), 2.42 (s, 3H), 3.29 (t, 2H), 4.29 (t, 2H), 5.21 (s, 2H), 5.58 (s, 2H), 6.92 (s, 1H), 7.22-7.31 (m, 3H), 7.40 (1H, bs), 7.47 (2H, m), 8.90 (s, 1H). MS ES ⁺ 547.2, 549.1 (M+H) ⁺ .
21		19			¹ H NMR δ (d ₆ -DMSO): 2.35 (s, 3H), 2.93 (s, 6H), 3.22 (m, 2H), 4.19 (m, 2H), 6.41 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 8.80 (s, 1H), 9.17 (s, 1H).
22		19			¹ H NMR δ (d ₆ -DMSO): 2.58 (m, 6H), 3.43 (t, 2H), 4.37 (t, 2H), 4.50 (d, 2H), 6.41 (m, 1H), 6.61 (m, 1H), 7.16 (m, 2H), 7.34-7.45 (m, 3H), 7.50 (m, 1H), 9.05 (s, 1H), 9.42 (s, 1H).
23		1	358		¹ H NMR δ (d ₆ -DMSO): 3.81 (s, 3H), 5.15 (s, 2H), 7.18 (t, 1H), 7.2-7.3 (m, 3H), 7.38 (d, 1H), 7.39-7.43 (m, 1H), 7.55 (t, 1H), 12.27 (br s, 1H).
24		20	363	361	¹ H NMR δ (d ₆ -DMSO): 2.35 (s, 3H), 3.2 (t, 2H), 4.2 (t, 2H), 6.55 (m, 1H), 7.05 (s, 1H), 7.2 (s, 1H), 8.81 (s, 1H), 9.2 (s, 1H), 9.8 (br s, 1H).

Example	Structure	Route	M _r	M _n	NMR
25		1b	336		
26		1b	405		
27		2a, 1c (b)	388	386	δ_H (500MHz, DMSO- d_6) 1.27 (6H, d), 4.73 (1H, m), 5.21 (2H, s), 6.82 (1H, s), 7.20-7.31 (3H, br m), 7.36- 7.47 (2H, br m), 7.58 (1H, t), 9.23 (1H, s), 12.97 (1H, br s).
28		2a, 1c (b)	389		δ_H (500MHz, DMSO- d_6) 1.28 (6H, d), 3.06 (2H, t), 4.27 (2H, t), 4.72 (1H, m), 6.72 (1H, s), 7.12 (1H, d), 7.26 (1H, s), 7.31 (2H, m), 7.48 (1H, m), 9.20 (1H, s).
29		2a, 1a (d)	434		δ_H (300MHz, DMSO- d_6) 1.26 (6H, d), 3.07 (2H, t), 4.15 (2H, t), 4.70 (1H, m), 6.68 (1H, s), 7.11 (1H, d), 7.22 - 7.34 (3H, br m), 7.47 (1H, m).
30		1b (HA TU)	402 .42	400 .39	δ_H (300MHz, DMSO- d_6) 1.27 (6H, d), 2.63 (3H, s), 4.70 (1H, hept), 5.20 (2H, s), 6.82 (1H, s), 7.24 (3H, m), 7.39 (2H, m), 7.56 (1H, t), 12.80 (1H, br s).
31		1b (HA TU)	404 .40	402 .37	δ_H (300MHz, DMSO- d_6) 1.27 (6H, d), 2.63 (3H, s), 3.06 (2H, t), 4.25 (2H, t), 4.70 (1H, hept), 6.72 (1H, s), 7.12 (1H, d), 7.28 (3H, m), 7.47 (1H, m), 12.77 (1H, br s).
32		1b (HA TU)	468 .39	466 .37	δ_H (300MHz, DMSO- d_6) 2.63 (3H, s), 5.23 (4H, s), 6.97 (1H, s), 7.24 (4H, m), 7.43 (4H, m), 7.57 (2H, t), 12.84 (1H, br s).

Example	Structure	Route	M _r H ₊	M _r H ₋	NMR
33		1a	336 .44	334 .40	

EXAMPLE II:

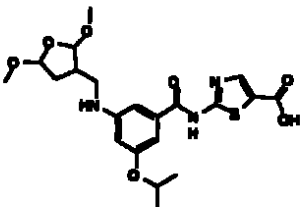
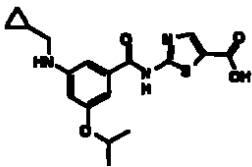
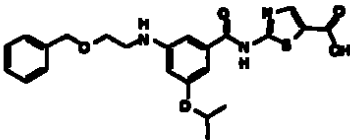
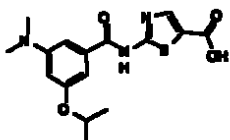
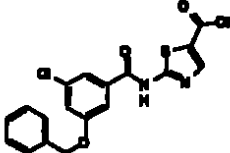
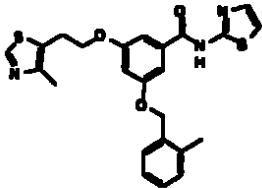
By analogous methods to those described above the following compounds, Example numbers 5 II₁ to II₁₆₆, were also made. Some compounds were prepared by Route 1b (multi-parallel synthesis), as described in Example T. For compounds made by Route 2a (hydrolysis of esters), the requisite starting materials may be prepared by Route 1 or 1b.

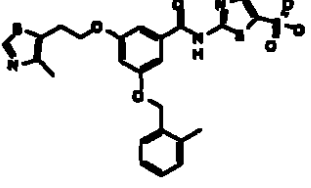
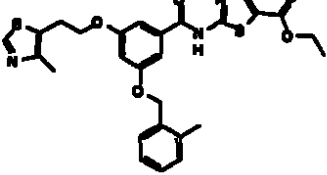
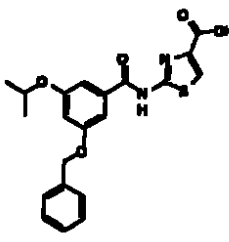
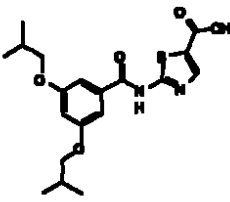
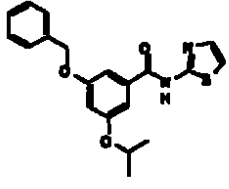
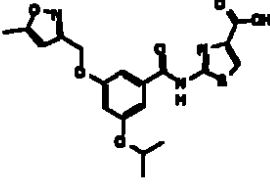
Example	Structure	Route	M _r H ₊	M _r H ₋	NMR
1		1	485, 487		¹ H NMR d (d6-DMSO): 5.24 (4H, s); 6.93 (1H, s); 7.26 (1H, d); 7.36-7.43 (6H, m); 7.50 (2H, m); 7.55 (1H, d); 7.61 (2H, m); 12.60 (1H, br s).
2		2a ****			¹ H NMR d (d6-DMSO): 5.25 (4H, s); 7.0 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.2 (1H, d).
3		1			¹ H NMR d (d6-DMSO): 3.62 (3H, s); 3.76 (2H, s); 5.24 (4H, s); 6.94 (1H, m); 7.06 (1H, s); 7.38-7.47 (6H, m); 7.54 (2H, m); 7.63 (2H, m); 12.69 (1H, br s).

Exemple	Structure	Route	M _r	NMR
4		1	531	¹ H NMR d (d6-DMSO): 4.77 (2H, s); 5.25 (4H, s); 6.94 (1H, m); 7.31 (1H, s); 7.36-7.48 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 12.83 (1H, br s) (+ 0.4 eq. iPr ₂ NEt).
5		3	528, 530	¹ H NMR d (d6-DMSO): 2.63 (3H, m); 4.16 (2H, m); 5.24 (4H, s); 6.99 (1H, s); 7.38-7.44 (7H, m); 7.52 (2H, m); 7.62 (2H, m); 9.06 (1H, br s); 12.75 (1H, br s).
6		3		¹ H NMR d (d6-DMSO): 2.57 (3H, m); 3.48 (2H, m); 5.25 (4H, s); 6.95 (2H, m); 7.36-7.44 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 7.83 (1H, m); 12.60 (1H, br s).
7		2a ****	497, 499 (-CO ₂)	¹ H NMR d (d6-DMSO): 3.64 (2H, s); 5.26 (4H, s); 6.95 (1H, s); 7.04 (1H, s); 7.37-7.46 (6H, m); 7.54 (2H, m); 7.63 (2H, m); 12.40 (1H, br s); 12.68 (1H, br s) (.HCl).
8		2a ****	459, 415 (-CO ₂)	¹ H NMR d (d6-DMSO): 5.15 (4H, s); 6.9 (1H, s); 7.2-7.5 (12H, m); 8.1 (1H, s).
9		1		¹ H NMR d (d6-DMSO): (iPr ₂ NEt salt) 1.24 (15H, m); 3.12 (2H, m); 3.80 (2H, m); 5.24 (4H, s); 6.93 (1H, m); 7.36-7.45 (7H, m); 7.51 (2H, m); 7.61 (2H, m); 12.56 (1H, br s).

Ex. No.	Structure	Yield %	mp °C	1H NMR
10		3		1H NMR d (d6-DMSO): 2.45 (4H, m); 3.55 (2H, s); 3.61 (4H, m); 5.29 (4H, s); 7.00 (1H, m); 7.11 (1H, s); 7.43-7.51 (6H, m); 7.58 (2H, m); 7.67 (2H, m); 12.86 (1H, br s).
11		4	550, 552	1H NMR d (d6-DMSO): 5.19 (2H, br s); 5.23 (4H, s); 6.72 (1H, dd); 6.93 (1H, m); 7.03 (1H, m); 7.35-7.44 (7H, m); 7.51 (2H, m); 7.61 (2H, m); 12.46 (1H, br s).
12		3	558, 560	1H NMR d (d6-DMSO): 2.60 (2H, t); 3.45 (2H, t); 3.72 (2H, s); 5.22 (4H, s); 6.91 (1H, m); 6.96 (1H, s); 7.35-7.30 (7H, m); 7.50 (2H, m); 7.60 (2H, m).
13		3	586, 588	1H NMR d (d6-DMSO): 3.11 (2H, q); 3.37 (2H, q); 3.50 (2H, s); 3.61 (1H, t); 5.22 (4H, s); 6.92 (2H, m); 7.34-7.42 (6H, m); 7.49 (2H, m); 7.60 (2H, m); 7.88 (1H, br s).
14		3	554, 556	1H NMR d (d6-DMSO): 0.29 (2H, m); 0.40 (2H, m); 2.16 (1H, m); 3.79 (2H, s); 5.27 (4H, s); 6.98 (2H, m); 7.40-7.48 (7H, m); 7.56 (2H, m); 7.66 (2H, m).
15		2b ****	366	364 1H NMR d (d6-DMSO): 7.05 (1H, d); 7.35 (1H, t); 7.45 (1H, dd); 7.6 - 7.75 (2H, m); 7.85 (1H, m); 7.9 - 8.0 (2H, m); 8.15 (1H, s); 13.1 (2H, br s).

Ex. No.	Structure	Yield (%)	mp (°C)	1H NMR (d6-DMSO)
16		6		1H NMR d (d6-DMSO): 2.68 (3H, s); 3.81 (1H, s); 5.15 (2H, s); 6.38 (1H, s); 6.87 (1H, s); 7.00 (1H, s); 7.37 (2H, m); 7.49 (1H, m); 7.58 (1H, m); 8.10 (1H, s); 8.21 (1H, s).
17		6		1H NMR d (d6-DMSO): 1.32 (6H, d); 4.88 (1H, m); 7.87 (1H, s); 8.05 (1H, s); 8.14 (1H, s); 8.45 (1H, s).
18		6	400, 402 (-CO2)	1H NMR d (d6-DMSO): 1.22 (6H, d); 4.36 (2H, m); 4.58 (1H, m); 6.24 (1H, s); 6.47 (1H, m); 6.84 (2H, m); 7.26 (3H, m); 7.37 (2H, m); 7.45 (1H, m); 7.76 (1H, br s).
19		6		1H NMR d (d6-DMSO): 1.21 (6H, d); 4.28 (2H, m); 4.55 (1H, m); 6.26 (1H, s); 6.43 (1H, m); 6.83 (1H, s); 6.89 (1H, s); 7.20 (1H, m); 7.26-7.37 (4H, m); 7.74 (1H, br s).
20		6	367 (-CO2)	1H NMR d (d6-DMSO): 1.23 (6H, d); 4.38 (2H, s); 4.60 (1H, m); 6.33 (1H, m); 6.89 (2H, m); 7.47 (1H, dd); 7.89 (1H, d); 8.10 (1H, s); 8.51 (1H, dd); 8.63 (1H, d).
21		6	396 (-CO2)	1H NMR d (d6-DMSO): 1.21 (6H, d); 3.81 (3H, s); 4.24 (2H, m); 4.55 (1H, m); 6.26 (2H, m); 6.84 (3H, m); 6.97 (1H, m); 7.20 (2H, m).

Ex. No.	Structure	Yield (%)	mp (°C)	IR (cm ⁻¹)
22		6		464, 420 (-CO ₂)
23		6		1H NMR d (d6-DMSO): 0.28 (2H, m); 0.52 (2H, m); 1.09 (1H, m); 1.32 (6H, d); 3.02 (2H, d); 4.69 (1H, m); 6.50 (1H, s); 6.99 (2H, s); 8.20 (1H, s).
24		6		1H NMR d (d6-DMSO): 1.24 (6H, d); 3.29 (2H, m); 3.56 (2H, t); 4.50 (2H, s); 4.58 (1H, m); 6.37 (1H, m); 6.85 (1H, s); 6.90 (1H, s); 7.26 (2H, m); 7.13 (3H, m); 8.10 (1H, s).
25		6		348 1H NMR d (d6-DMSO): 1.27 (6H, d); 2.96 (6H, s); 4.69 (1H, m); 6.39 (1H, m); 6.97 (1H, s); 7.04 (1H, s); 8.13 (1H, s); 12.89 (1H, br s).
26		2a ****	389, 391	1H NMR d (d6-DMSO): 5.21 (2H, s); 7.29-7.49 (6H, m); 7.74 (2H, s); 8.13 (1H, s); 13.1 (1H, br s).
27		1		1H NMR d (d6-DMSO): 2.31 (3H, s); 2.35 (3H, s); 3.22 (2H, t); 4.21 (2H, t); 5.12 (2H, s); 6.79 (1H, m); 7.18-7.28 (4H, m); 7.30 (1H, m); 7.54 (1H, d); 8.82 (1H, s); 12.48 (1H, br s).

Example	Structure	Yield	Mp	NMR
28		1		¹ H NMR d (d ₆ -DMSO): 2.32 (3H, s); 2.37 (3H, s); 3.24 (2H, t); 4.22 (2H, t); 5.13 (2H, s); 6.80 (1H, m); 7.19 (3H, m); 7.29 (1H, s); 7.37-7.45 (3H, m); 9.06 (1H, s); 12.48 (1H, br s).
29		1		¹ H NMR d (d ₆ -DMSO): 1.28 (3H, t); 2.32 (3H, s); 2.37 (3H, s); 3.24 (2H, t); 4.14-4.29 (4H, m); 5.13 (2H, s); 6.84 (1H, m); 7.21 (4H, m); 7.29 (1H, s); 7.38 (2H, m); 8.20 (1H, s); 8.81 (1H, s).
30		2a (1)		¹ H NMR d (d ₆ -DMSO): 1.26 (d, 6H), 4.69 (m, 1H), 5.14 (s, 2H), 6.75 (s, 1H), 7.26-7.48 (m, 7H), 8.01 (s, 1H).
31		2a (1b)	391	¹ H NMR d (d ₆ -DMSO): 1.0 (d, 12H), 2.0 (m, 2H), 3.8 (d, 4H), 6.75 (s, 1H), 7.25 (d, 2H), 8.15 (s, 1H).
32		1		¹ H NMR δ (d ₆ -DMSO): 1.26 (d, 6H), 4.69 (m, 1H), 5.16 (s, 2H), 6.74 (s, 1H), 7.26 (d, 1H), 7.31-7.47 (m, 7H), 8.54 (d, 1H), 12.47 (bs, 1H).
33		2a (1)		¹ H NMR δ (d ₆ -DMSO): 1.26 (d, 6H), 2.38 (s, 3H), 4.69 (m, 1H), 5.18 (s, 2H), 6.31 (s, 1H), 6.76 (s, 1H), 7.30 (s, 1H), 7.35 (s, 1H), 8.00 (s, 1H).

Example	Structure	Route	1M- H ⁺	1M- H ⁻	NMR
34		2a (1)			¹ H NMR δ (d ₆ -DMSO): 1.26 (d, 6H), 2.39 (s, 3H), 4.70 (m, 1H), 5.20 (s, 2H), 6.31 (s, 1H), 6.79 (s, 1H), 7.27 (s, 1H), 7.32 (s, 1H), 8.12 (s, 1H).
35		1b	397		
36		1b	401		
37		1			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 2.39 (s, 3H), 4.69 (m, 1H), 5.18 (s, 2H), 6.31 (s, 1H), 6.76 (s, 1H), 7.26 (m, 2H), 7.32 (s, 1H), 8.53 (d, 1H).
36		2a (1)	379	377	¹ H NMR δ (d ₆ -DMSO): 12.98(bs, 1H), 8.12 (s, 1H), 7.24(s, 1H), 6.66(s, 1H), 4.70(m, 1H), 3.79 (d, 2H), 2.01 (m, 1H), 1.28 (d, 6H), 0.98 (d, 6H).
37		2a (1b)	365		¹ H NMR d (d ₆ -DMSO): 1.25 (d, 12H), 4.7 (hept, 2H), 6.65 (s, 1H), 7.2 (s, 2H), 8.15 (s, 1H).
38		2a (1)			¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.16 (s, 4H), 6.90 (s, 1H), 7.29-7.47 (m, 7H), 7.53 (s, 1H), 8.03 (m, 1H), 12.90 (bs, 1H).

Example	Structure	Yield (%)	mp (°C)	¹ H NMR
39		2a (1)		¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.17 (s, 4H), 6.93 (s, 1H), 7.29-7.45 (m, 7H), 7.53 (s, 1H), 8.13 (m, 1H).
40		1		¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.14 (s, 4H), 6.90 (s, 1H), 7.26 (d, 1H), 7.31-7.47 (m, 7H), 7.49 (m, 1H), 7.55 (d, 1H), 12.56 (bs, 1H).
41		1b	349	
42		2a (1)		¹ H NMR δ (d ₆ -DMSO): 5.22 (s, 4H), 6.96 (s, 1H), 7.20-7.29 (m, 4H), 7.37-7.44 (m, 4H), 7.55 (m, 2H), 8.12 (s, 1H).
43		2a (1)		¹ H NMR δ (d ₆ -DMSO): 5.21 (s, 4H), 6.93 (s, 1H), 7.19-7.29 (m, 4H), 7.38-7.46 (m, 4H), 7.56 (m, 2H), 8.03 (s, 1H).
44		2a (1)		¹ H NMR δ (d ₆ -DMSO): 2.38 (s, 3H), 3.25 (t, 2H), 4.24 (t, 2H), 4.65 (d, 2H), 5.27 (d, 1H), 5.42 (d, 1H), 6.05 (m, 1H), 6.78 (s, 1H), 7.32 (s, 2H), 8.15 (s, 1H), 8.90 (s, 1H), 12.94 (br s, 1H).
45		2a (1)		¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.34 (s, 3H), 3.22 (t, 2H), 4.21 (t, 2H), 5.13 (s, 2H), 6.82 (s, 1H), 7.16-7.25 (m, 3H), 7.30 (1H, s), 7.39 (1H, m), 7.98 (s, 1H), 8.81 (s, 1H).

Exemplar	Structure	Route	mp °C	mw g/mol	NMR
46		2a *	419	417	¹ H NMR δ (d ₆ -DMSO): 3.8 (s, 3H), 5.3 (s, 2H), 7.15 (dd, 1H), 7.2-7.4 (m, 4H), 7.5 (d, 1H), 7.6 (d, 1H), 8.0 (s, 1H).
47		2a *	427	425	¹ H NMR δ (d ₆ -DMSO): 1.1 (d, 6H), 2.85 (hept, 1H), 3.75 (s, 3H), 5.2 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (d, 1H), 8.0 (s, 1H).
48		2a **	405	403	¹ H NMR δ (d ₆ -DMSO): 2.34 (s, 3H), 3.20 (t, 2H), 4.13 (t, 2H), 6.43 (s, 1H), 6.92 (s, 1H), 6.97 (s, 1H), 8.09 (s, 1H), 8.83 (s, 1H), 12.75 (bs, 1H).
49		2a *			¹ H NMR δ (d ₆ -DMSO): 2.33 (s, 3H), 2.36 (2.36, 3H), 3.23 (t, 2H), 4.22 (t, 2H), 5.15 (s, 2H), 7.21 (s, 1H), 7.02-7.44 (m, 6H), 8.13 (s, 1H), 8.85 (s, 1H), 12.92 (bs, 1H).
50		6 **			¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.34 (s, 3H), 3.19 (t, 2H), 4.12 (t, 2H), 4.25 (s, 2H), 6.37 (s, 1H), 6.92 (d, 2H), 7.08-7.21 (m, 3H), 7.25 (dd, 1H), 8.10 (s, 1H), 8.85 (s, 1H), 12.76 (bs, 1H).
51		6 **			
52		1			¹ H NMR δ (d ₆ -DMSO): 1.28 (t, 3H), 2.35 (s, 3H), 3.22 (t, 2H), 4.11 (t, 2H), 4.27 (q, 2H), 4.63 (d, 2H), 5.26 (dd, 1H), 5.39 (d, 1H), 6.04 (m, 1H), 6.76 (t, 1H), 7.28 (d, 2H), 8.21 (s, 1H), 8.81 (s, 1H), 13.02 (bs, 1H).
53		1b	261	259	¹ H NMR δ (CDCl ₃): 4.58 (d, 2H), 5.31 (dd, 1H), 5.45 (dd, 1H), 6.04 (m, 1H), 6.95 (d, 1H), 7.11 (d, 1H), 7.18 (m, 1H), 7.41 (t, 1H), 7.55 (m, 2H), 12.09 (br s, 1H).

Ex. no.	Structure	Mass	¹ H	¹³ C	NMR
54		2a	445		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.98–2.05 (m, 1H), 3.81 (d, 2H), 5.20 (s, 2H), 6.81 (s, 1H), 7.0–7.1 (m, 2H), 7.35 (s, 1H), 7.38–7.45 (m, 2H), 7.58 (t, 1H), 8.03 (s, 1H), 12.90 (br s, 1H).
55		2a	441		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.98–2.05 (m, 1H), 2.36 (s, 3H), 3.81 (d, 2H), 5.17 (s, 2H), 6.81–7.17–7.23 (m, 3H), 7.32 (s, 1H), 7.40 (ap d, 2H), 8.01 (s, 1H).
56		2a			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 4.71 (sept, 1H), 5.16 (d, 2H), 6.78 (d, 1H), 7.25–7.51 (m, 7H), 8.12 (s, 1H), 12.98 (bs, 1H).
57		2a	434	432	¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.98–2.05 (m, 1H), 3.81 (d, 2H), 5.26 (s, 2H), 6.83 (ap t, 1H), 7.30 (s, 1H), 7.39 (s, 1H), 7.79 (s, 1H), 8.12 (s, 1H), 9.1 (s, 1H).
58		1b	335		
59		1b	293		
60		1			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.74 (sept, 1H), 5.22 (s, 2H), 6.79 (t, 1H), 7.19–7.32 (m, 4H), 7.37 (t, 1H), 7.43 (m, 1H), 7.56 (m, 2H), 12.61 (bs, 1H).
61		2a			¹ H NMR δ (d ₆ -DMSO) 1.26 (d, 6H), 4.64–4.76 (m, 1H), 5.20 (s, 2H), 6.78 (s, 1H), 7.18–7.34 (m, 3H), 7.36–7.46 (m, 2H), 7.50–7.60 (m, 1H), 7.98 (s, 1H).

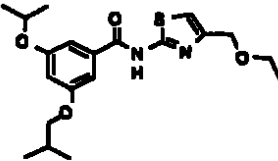
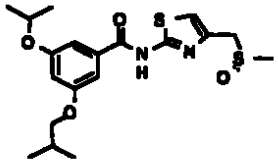
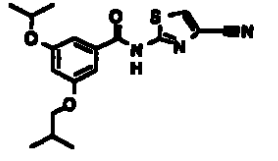
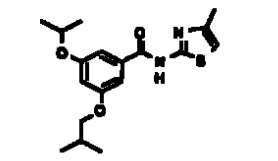
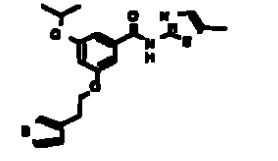
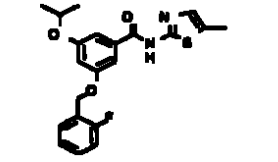
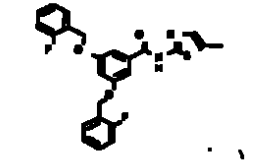
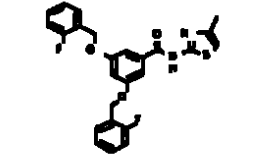
Ex. no.	Structure	Route	mp °C	MS m/z	NMR
62		2a			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 4.71 (m, 1H), 5.20 (s, 2H), 6.78-6.84 (m, 1H), 7.18-7.31 (m, 3H), 7.34-7.49 (m, 2H), 7.52-7.61 (m, 1H), 8.12 (s, 1H), 12.98 (bs, 1H)
63		2a	377		¹ H NMR δ (d ₆ -DMSO): 0.0-0.2 (m, 2H), 0.22-0.3 (m, 2H), 0.98 (d, 6H), 3.59 (d, 2H), 4.35-4.42 (m, 1H), 6.4 (s, 1H), 6.93 (s, 2H), 7.82 (s, 1H).
64		2a	403		¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.78 (m, 1H), 4.86 (q, 2H), 6.89 (ap t, 1H), 7.36 (ap t, 2H), 8.17 (s, 1H), 13.05 (bs)
65		1 ***			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.72 (m, 1H), 5.19 (s, 2H), 6.88-6.97 (m, 1H), 7.09 (m, 1H), 7.16-7.26 (m, 4H), 7.54 (d, 1H), 7.61 (s, 1H), 7.70 (s, 1H), 12.05 (bs, 1H).
66		2a ***			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.74 (m, 1H), 5.18 (s, 2H), 6.87-6.97 (m, 1H), 7.11 (m, 1H), 7.16-7.26 (m, 3H), 7.63 (s, 1H), 7.71 (s, 1H), 8.11 (s, 1H).
67		2a ***			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.74 (m, 1H), 5.18 (s, 2H), 6.89-6.97 (m, 1H), 7.09 (m, 1H), 7.17-7.26 (m, 3H), 7.66 (s, 1H), 7.74 (s, 1H), 7.99 (s, 1H).
68		1b	457		
69		1b	404		
70		23			¹ H NMR δ (d ₆ -DMSO): 1.28 (d, 6H), 4.51 (s, 2H), 4.71 (m, 1H), 7.05 (s, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 7.53 (d, 1H), 7.58 (s, 1H), 12.50 (bs, 1H).

Example	Structure	Route	M _r	M _n	NMR
71		2a	405	403	¹ H NMR δ (d ₆ -DMSO): 1.14 (d, 6H), 1.3-1.4 (m, 2H), 1.42-1.62 (m, 4H), 1.65-1.82 (m, 2H), 3.9 (d, 2H), 4.62-4.78 (m, 1H), 6.68 (s, 1H), 7.22 (s, 2H), 8.12 (s, 1H).
72		2a	381	379	¹ H NMR δ (d ₆ -DMSO): 1.25 (d, 6H), 3.3 (s, 3H), 3.7 (t, 2H), 4.15 (t, 2H), 4.6-4.8 (hept, 1H), 6.75 (t, 1H), 7.25 (d, 2H), 8.15 (s, 1H), 13.0 (bs, 2H).
73		2a	379	377	¹ H NMR δ (d ₆ -DMSO): 3.85 (s, 3H), 5.25 (s, 2H), 6.9 (m, 1H), 7.2-7.35 (m, 3H), 7.4-7.5 (m, 2H), 7.6-7.7 (t of d, 1H), 8.15 (s, 1H), 13.0 (bs, 2H).
74		2a	401		¹ H NMR δ (d ₆ -DMSO): 0.9 (t, 3H), 1.2-1.3 (d, 3H + d, 6H), 1.5-1.75 (m, 2H), 4.45 (hex, 1H), 4.75 (hept, 1H), 6.7 (t, 1H), 7.2 (d, 2H), 8.15 (s, 1H), 13.0 (bs, 2H).
75		22			¹ H NMR δ (d ₆ -DMSO): 1.31 (d, 6H), 4.82 (m, 1H), 7.26 (d, 1H), 7.56 (d, 1H), 7.59 (s, 1H), 7.94 (d, 1H), 8.15 (s, 1H), 10.00 (s, 1H), 12.77 (bs, 1H).
76		2a			¹ H NMR δ (d ₆ -DMSO): 0.97 (d, 3H), 1.26 (s, 6H), 1.72 (t, 2H), 3.85-4.20 (m, 2H), 4.56-4.83 (m, 1H), 6.69 (s, 1H), 7.00 (s, 1H), 7.26 (s, 1H), 8.11 (s, 1H).
77		2a	359		¹ H NMR δ (d ₆ -DMSO): 1.30 (d, 6H), 3.30 (s, 1H), 4.74 (m, 1H), 4.88 (s, 2H), 6.80 (s, 1H), 7.31 app d, 2H), 8.15 (s, 1H), 10.01 (bs, 1H).
78		2a	407	405	¹ H NMR δ (d ₆ -DMSO): 0.91 (t, 6H), 1.29 (d, 6H), 1.37-1.53 (m, 4H), 1.56-1.70 (m, 1H), 3.30 (d, 2H), 4.73 (m, 1H), 6.72 (s, 1H), 7.26 (app d, 2H), 8.14 (s, 1H), 13.00 (bs, 1H).

Ex. no.	Structure	Route	MP	MM	NMR
79		1	378		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.28 (d, 6H), 2.02 (m, 1H), 3.80 (d, 2H), 4.65 (m, 1H), 6.75 (ap t, 1H), 7.25 (ap d, 2H), 8.68 (s, 1H)
80		28	533		¹ H NMR δ (d ₆ -DMSO): 1.22 (d, 6H), 1.61 (s, 6H), 4.58-4.64 (m, 1H), 6.62 (s, 1H), 7.19 (s, 1H), 7.40 (s, 1H), 8.05 (s, 1H), 8.12 (s, 1H).
81		2a			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.50 (m, 2H), 4.71 (m, 1H), 5.26 (bs, 1H), 7.08 (s, 1H), 7.53 (s, 1H), 7.60 (s, 1H), 8.01 (s, 1H), 13.00 (bs, 1H).
82		21			¹ H NMR δ (d ₆ -DMSO): 1.32 (d, 6H), 2.80 (s, 3H), 3.37-3.63 (m, 4H), 3.95-4.10 (m, 4H), 4.39 (m, 2H), 4.76 (m, 1H), 7.29 (d, 1H), 7.53 (m, 3H), 7.68 (s, 1H), 7.79 (s, 1H), 12.77 (bs, 1H).
83		21			¹ H NMR δ (d ₆ -DMSO): 1.31 (d, 6H), 2.71 (s, 6H), 4.26 (m, 2H), 4.76 (m, 1H), 7.29 (d, 1H), 7.42 (m, 1H), 7.55 (d, 1H), 7.70 (s, 1H), 10.66 (bs, 1H).
84		21			¹ H NMR δ (d ₆ -DMSO): 1.31 (d, 6H), 3.03-3.16 (m, 4H), 3.71-3.95 (m, 4H), 4.34 (m, 2H), 4.77 (m, 1H), 7.47 (m, 1H), 7.72 (m, 2H), 8.13 (s, 1H).
85		21			¹ H NMR δ (d ₆ -DMSO): 0.41 (m, 2H), 0.60 (m, 2H), 1.14 (m, 1H), 1.35 (d, 6H), 2.85 (m, 2H), 4.19 (m, 2H), 4.81 (m, 1H), 7.32 (d, 1H), 7.46 (s, 1H), 7.60 (d, 1H), 7.72 (s, 1H), 7.80 (s, 1H), 9.35 (bs, 2H).
86		21			¹ H NMR δ (d ₆ -DMSO): 1.27 (m, 12H), 3.26 (m, 2H), 4.14 (m, 2H), 4.76 (m, 1H), 7.26 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H), 7.68 (s, 1H), 7.76 (s, 1H), 9.18 (bs, 2H).

Example	Structure	Page	1a	1b	NMR
87		21			¹ H NMR δ (d ₆ -DMSO): 0.72 (m, 2H), 0.89 (m, 2H), 1.32 (d, 6H), 2.66 (m, 1H), 4.21 (m, 2H), 4.75 (m, 1H), 7.26 (d, 1H), 7.42 (s, 1H), 7.55 (d, 1H), 7.68 (s, 1H), 7.76 (s, 1H), 9.53 (bs, 2H).
88		1 (See Ex 26)	351	349	¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 3.70 (s, 3H), 4.71 (m, 1H), 4.86 (s, 2H), 6.99 (t, 1H), 7.23 (t, 1H), 7.26-7.27 (m, 2H), 12.53 (s, 1H).
89		24			¹ H NMR δ (d ₆ -DMSO): 1.32 (d, 6H), 4.79 (m, 1H), 7.62 (m, 1H), 7.92 (m, 1H), 8.13 (s, 1H), 8.18 (s, 1H), 10.03 (s, 1H).
90		26	419	417	¹ H NMR δ (d ₆ -DMSO): 1.28 (d, 6H), 2.18 (s, 3H), 2.24 (m, 2H), 2.32 (m, 2H), 3.44 (ap t, 4H), 4.65 (m, 1H), 4.85 (s, 2H), 6.68 (ap t, 1H), 7.19 (m, 1H), 7.24 (ap d, 2H), 7.55 (ap d, 1H), 12.45 (bs, 1H).
91		25			¹ H NMR δ (d ₆ -DMSO): 1.01 (d, 6H), 1.29 (d, 6H), 2.81 (m, 1H), 4.72 (m, 1H), 6.53 (dd, 1H), 6.29 (d, 1H), 6.97 (s, 1H), 7.50 (s, 1H), 7.53 (s, 1H), 8.11 (s, 1H), 8.18 (s, 1H).
92		1			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 9H), 4.28 (q, 2H), 4.53 (d, 2H), 4.71 (m, 1H), 5.26 (t, 1H (-OH)), 7.10 (s, 1H), 7.53 (s, 1H), 7.60 (s, 1H), 8.20 (s, 1H), 13.01 (bs, 1H).
93		1			¹ H NMR δ (d ₆ -DMSO): 1.34 (d, 3H), 1.39 (m, 6H), 4.30 (q, 2H), 4.84 (m, 1H), 7.58 (s, 1H), 7.97 (s, 1H), 8.17 (s, 1H), 8.26 (s, 1H), 10.09 (s, 1H).
94		1a	307		

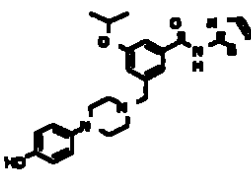
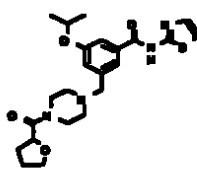
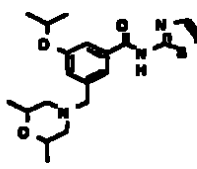
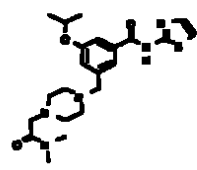
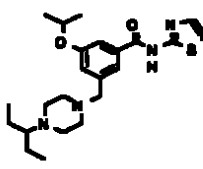
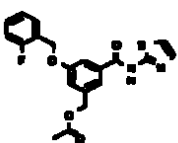
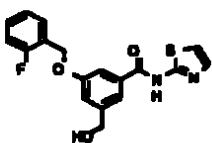
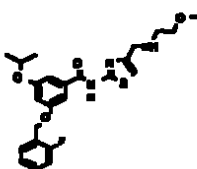
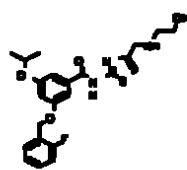
Example	Structure	Route	MS + H ⁺	MS - H ⁺	NMR
95		1a	307.		
96		2a, 1c	389	387	δ_H (300MHz, DMSO- d_6) - 0.04-0.06 (4H,m); 0.22-0.35 (4H,m); 0.85-1.05 (2H,m); 3.54-4.64 (4H,d); 6.44 (1H, m); 6.93 (6.93-6.97 (2H, m); 7.84 (1H, s)
97		1b (HA TU)	389 .38	387 .34	δ_H (300MHz, DMSO- d_6) 1.30 (6H, d), 3.08 (2H, t), 4.25 (2H, t), 4.73 (1H, hept), 6.70 (1H, s), 7.14 (1H, d), 7.3 (4H, m), 7.48 (1H, m), 7.57 (1H, d), 12.55 (1H, br s).
98		1a	349		
99		1b (HA TU)	374 .43	372 .39	δ_H (300MHz, DMSO- d_6) 0.98 (6H, d), 1.27 (6H, d), 2.00 (1H, m), 3.80 (2H, d), 4.24 (2H, s), 4.70 (1H, hept), 6.66 (1H, t), 7.23 (2H, d), 7.46 (1H, s), 12.59 (1H, br s).
100		1a	401		
101		1a	415		
102		3 (e) (CM 1a)	395 .19	393 .19	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.35 (6H, d), 2.08 (4H, m), 3.74 (4H, m), 4.60 (1H, hept), 6.64 (1H, m), 6.78 (1H, s), 7.00 (1H, m).

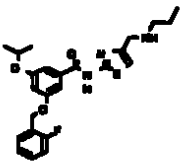
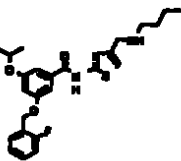
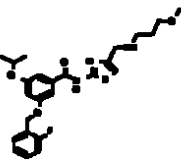
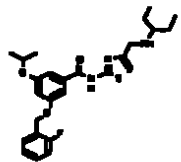
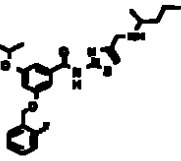
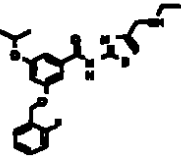
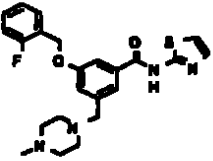
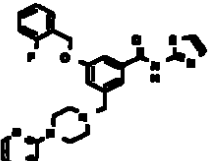
Example	Structure	Route	MS M ⁺	MS M ⁺	MS M ⁺
103		3 (e) (CM 1a)	393 .22	391 .21	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.26 (3H, t), 1.35 (6H, d), 2.08 (1H, m), 3.60 (2H, q), 3.74 (d, 2H), 4.47 (2H, s), 4.58 (1H, hept), 6.64 (1H, m), 6.88 (1H, s), 7.02 (1H, m).
104			411 .42	409 .38	δ_H (300MHz, DMSO-d ₆) 0.98 (6H, d), 1.27 (6H, d), 2.02 (1H, m), 2.55 (3H, s), 3.80 (2H, d), 4.14 (2H, s), 4.70 (1H, hept), 6.66 (1H, s), 7.23 (3H, m), 12.62 (1H, br s).
105		1a	427 .39	425 .38	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.36 (6H, d), 2.08 (1H, m), 3.75 (2H, d), 4.60 (1H, hept), 6.68 (1H, m), 7.00 (2H, m), 7.69 (1H, s).
106		1b (HA TU)	349 .45	347 .43	δ_H (300MHz, CDCl ₃) 0.95 (6H, d), 1.25 (6H, d), 1.95-2.05 (1H, m), 2.2 (3H, s), 3.65 (2H, d), 6.7 (1H, m), 6.98 (1H, m), 7.02 (1H, m).
107		1b (HA TU)	403 .39	401 .37	δ_H (300MHz, DMSO-d ₆) 1.25 (6H, d), 2.38 (3H, s), 3.05 (2H, t), 4.6-4.8 (1H, m), 7.05 (1H, d), 7.10-7.12 (3H, m), 7.15, (1H, m), 7.42-7.45 (1H, m).
108		1b (HA TU)	401 .42	399 .39	δ_H (300MHz, CDCl ₃) 1.25 (6H, d), 2.3 (3H, s), 4.4-4.6 (1H, m), 5.05 (2H, s), 6.65 (1H, m), 6.85 (1H, s), 7.0-7.15 (4H, m), 7.2-7.3 (1H, m), 7.38-7.42 (1H, m).
109		1b (HA TU)	467 .38	465 .37	δ_H (300MHz, DMSO-d ₆) 2.35 (3H, s), 5.2 (4H, s), 6.95 (1H, s), 7.2-7.3 (5H, m), 7.4-7.45 (4H, m), 7.5-7.6 (2H, m).
110		1b (HA TU)	467 .37	465 .38	δ_H (300MHz, CDCl ₃) 1.9 (3H, s), 4.95 (4H, s), 6.4 (1H, s), 6.9-7.1 (6H, m), 7.15-7.25 (2H, m), 7.3-7.4 (2H, m).

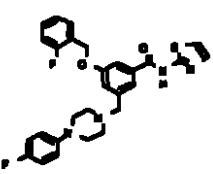
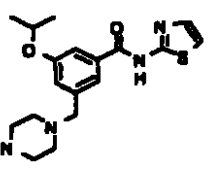
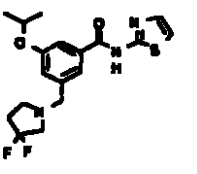
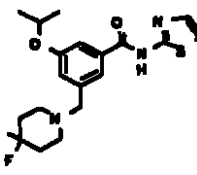
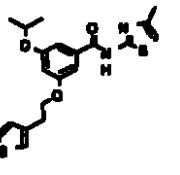
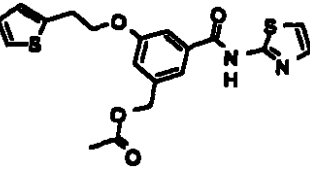
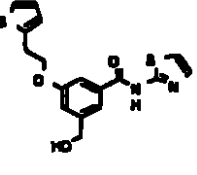
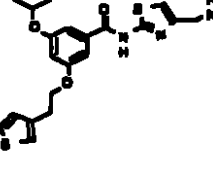
Example	Structure	Figure	¹³ C- NMR	¹ H- NMR	MS
111		2a, 1a	433	431	δ_H (500MHz, DMSO-d ₆) 1.27 (6H, d), 3.06 (2H, t), 4.25 (2H, t), 4.72 (1H, m), 6.71 (1H, s), 7.12 (1H, d), 7.23-7.32 (3H, br m), 7.46 (1H, m), 8.10 (1H, s).
112		2a, 1a	433	431	δ_H (500MHz, DMSO-d ₆) 1.28 (6H, d), 3.06 (2H, t), 4.24 (2H, t), 4.72 (1H, m), 6.69 (1H, s), 7.12 (1H, d), 7.27 (1H, s), 7.31 (2H, s), 7.47 (1H, m), 8.02 (1H, s).
113		21	439 .44	437 .39	δ_H (300MHz, DMSO-d ₆) 1.25 (6H, d), 3.0-3.2 (2H, m), 3.3-3.55 (4H, m), 4.3-4.5 (4H, m), 4.75-4.85 (1H, m), 7.25 (1H, d), 7.55-7.6 (2H, m), 7.65 (1H, s), 7.75 (1H, s), 7.95 (1H, s), 8.1 (1H, s), 8.4 (1H, s).
114		3	430 .40	428 .38	δ_H (300MHz, CDCl ₃) 1.25 (6H, d), 2.42 (3H, s), 3.82 (2H, s), 4.45-4.6 (1H, m), 5.05 (2H, s), 6.6 (1H, s), 6.95-7.15 (3H, m), 7.2-7.25 (2H, m), 7.35-7.45 (1H, m).
115		3	474 .42	472 .40	
116		21	419 .47	417 .44	δ_H (300MHz, DMSO-d ₆) 1.25 (6H, d), 3.25 (3H, s), 3.3-3.75 (12H, m), 4.3-4.45 (2H, m), 4.75-4.8 (1H, m), 7.25 (1H, d), 7.5-7.6 (2H, m), 7.7 (1H, s), 7.8 (1H, s).
117		21	453 .39	451 .37	
118		3	458 .39	456 .42	

Entry No.	Structure	Rate	M _r	M _n	NMR
119		21	495 .43		δ_H (300MHz, DMSO-d ₆) 1.25 (6H, d), 3.3-3.65 (8H, m), 4.2-4.5 (2H, m), 4.7-4.8 (1H, m), 6.05 (2H, s), 6.95 (1H, d), 7.05 (1H, d), 7.25 (2H, m), 7.55 (2H, m), 7.7 (1H, s), 7.8 (1H, s).
120		3	490 .43	488 .42	
121		3	470 .48	468 .47	
122		3	488 .49	486 .47	
123		3	486 .51	484 .51	
124		21	467 .50	465 .49	
125		21	455 .48 453 .46		
126		21	467 .50	465 .48	

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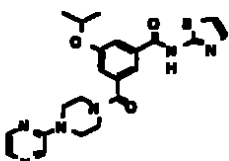
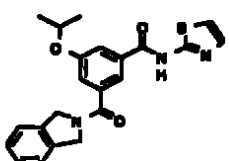
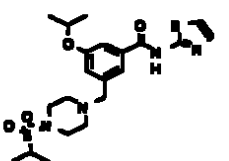
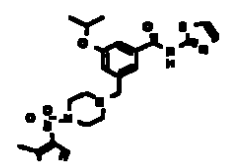
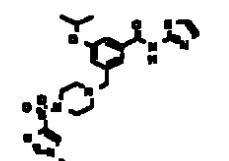
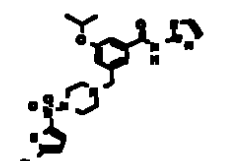
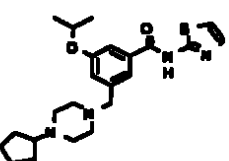
Example	Structure	MS m/z	MS m/z	MS m/z	
127		21	453 .49	451 .47	
128		21	459 .49	457 .47	
129		21	390 .51	388 .47	
130		21	446 .51	444 .49	
131		21	431 .55	429 .51	
132		1b (HA TU)	401 .37	399 .33	δ_H (300MHz, DMSO- d_6) 2.08 (3H, s), 5.12 (2H, s), 5.24 (2H, s), 7.23 (4H, m), 7.42 (1H, m), 7.56 (2H, m), 7.68 (1H, s), 7.76 (1H, s), 12.64 (1H, br s).
133		2a (f)	359 .43	357 .39	δ_H (300MHz, DMSO- d_6) 4.55 (2H, d), 5.23 (2H, s), 7.23 (4H, m), 7.42 (1H, m), 7.56 (2H, m), 7.68 (2H, m), 12.56 (1H, br s).
134		3	474 .48	472 .47	
135		3	460 .46	458 .43	

Example	Structure	Route	MP °C	MP °C	NMR
136		3	458 .48	456 .47	
137		3	472 .51	470 .49	
138		3	488 .51	486 .52	
139		3	486 .49	484 .47	
140		3	486 .50	484 .49	
141		3	444 .45	442 .41	
142		21	441 .43	439 .42	δ_H (300MHz, DMSO- d_6) 2.82 (3H, s), 3.49 (8H, m), 4.54 (1H, d), 5.24 (3H, m), 7.30 (3H, m), 7.45 (2H, m), 7.59 (2H, m), 7.81 (2H, m), 12.65 (1H, br s).
143		21	505 .45	503 .38	δ_H (300MHz, DMSO- d_6) 3.15 (2H, m), 3.45 (2H, m), 4.25 (4H, m), 4.52 (1H, d), 5.25 (3H, m), 7.27 (3H, m), 7.45 (1H, m), 7.62 (3H, m), 7.90 (3H, m), 8.16 (1H, s), 8.42 (1H, s), 12.70 (1H, br s).

Example	Structure	Route	M _r	M _n	NMR
144		21	521.43		δ_H (300MHz, DMSO- d_6) 3.33 (8H, m), 4.52 (1H, d), 5.27 (3H, m), 7.03 (5H, m), 7.28 (3H, m), 7.45 (1H, m), 7.65 (3H, m), 7.89 (1H, m), 9.20 (1H, br s), 12.69 (1H, br s).
145		21	361.50	359.46	δ_H (300MHz, CDCl ₃) 1.36 (6H, d), 2.56 (4H, m), 3.04 (4H, m), 3.53 (2H, s), 4.61 (1H, hept), 6.95 (1H, d), 7.07 (1H, m), 7.24 (1H, m), 7.44 (2H, m).
146		21	382.12	380.13	^1H NMR δ (CDCl ₃): 1.37 (d, 6H), 2.3 (m, 2H), 2.7 (m, 2H), 2.7 (m, 2H), 2.85 (m, 2H), 4.6 (m, 1H), 6.95 (m, 1H), 7.1 (m, 1H), 7.2 (m, 1H), 7.4 (m, 2H)
147		21	396.45	394.4	^1H NMR δ (CDCl ₃): 1.37 (d, 6H), 1.95 (m, 4H), 2.5 (m, 4H), 3.55 (s, 2H), 4.6 (m, 1H), 7.0 (d, 1H), 7.1 (m, 1H), 7.6 (m, 1H)
148		1b (HAT U)	382.12	380.13	^1H NMR δ (CDCl ₃): 1.37 (d, 6H), 2.3 (m, 2H), 2.7 (m, 2H), 2.7 (m, 2H), 2.85 (m, 2H), 4.6 (m, 1H), 6.95 (m, 1H), 7.1 (m, 1H), 7.2 (m, 1H), 7.4 (m, 2H)
149		1b (HAT U)	403.39	401.36	δ_H (300MHz, DMSO- d_6) 2.09 (3H, s), 3.26 (2H, t), 4.30 (2H, t), 5.08 (2H, s), 6.98 (2H, m), 7.17 (1H, s), 7.26 (1H, d), 7.35 (1H, m), 7.54 (1H, d), 7.64 (2H, br s), 12.62 (1H, br s).
150		2a (g)	361.41	359.38	
151		3	432.40	430.37	

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64

Example	Structure	Yield	M _n g/mol	M _w g/mol	MP
152		3	476 .48	474 .47	
153		3	472 .48	470 .45	
154		3	462 .45	460 .43	
155		21	462 .41	460 .38	
156		21	521 .42	519 .40	
157		21	507 .48		
158		21	453 .52	451 .49	¹ H NMR δ (CDCl ₃): 1.35 (d, 6H), 2.5 ((m, 2H), 3.65 (m, 4H), 4.65 (m, 1H), 6.3 (d, 1H), 6.95 (d, 1H), 7.1 (m, 1H), 7.35 (d, 1H), 7.5 (m, 1H), 7.58 (s, 1H), 8.1 (d, 1H)
159		21	461 .49	459 .48	

Example	Structure	Route	M _r	M _r	NMR
160		1b (HAT U) (h)	453 .44	451 .40	
161		1b (HAT U) (h)	406 .40		
162		21 (i)	467 .50	465 .49	
163		21 (i)	506 .47	504 .46	
164		21 (i)	505 .46	503 .43	
165		21 (i)	541 .39	539 .35	
166		21	429 .54	427 .51	

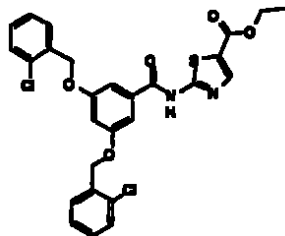
Notes:

* Final products prepared by hydrolysis method 2a; requisite starting materials prepared according to generic alkylation methodology followed by coupling (Route 1).

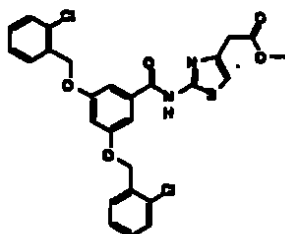
** Final products prepared by reductive amination method 6 method ; requisite starting materials prepared according to generic alkylation methodology followed by coupling (Route 1) and hydrolysis (Route 2a).

*** Final products prepared by hydrolysis (Route 2a) or acid chloride coupling (Route 1); requisite starting materials prepared according to generic alkylation methodology followed by coupling (Route 1).

5 **** For Examples II₂, II₇, II₈, II₁₅ and II₂₆, the ester intermediates were prepared by route 1:

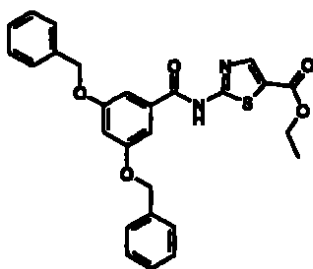


¹H NMR δ (d₆-DMSO): 1.3 (3H, t); 4.3 (2H, q); 5.25 (4H, s); 7.0 (1H, t); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.2 (1H, s).

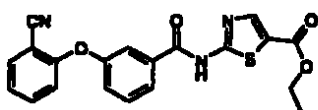


exemplified as Example II₃.

10

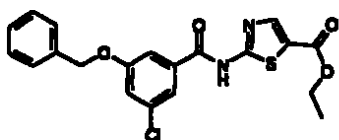


¹H NMR δ (d₆-DMSO): 1.3 (3H, t); 4.3 (2H, q); 5.2 (4H, s); 6.95 (1H, t); 7.2-7.5 (12H, m); 8.2 (1H, s); 13.05 (1H, br s); the spectrum also contains signals due to trace amounts of 2-aminothiazole.



15

not characterised.

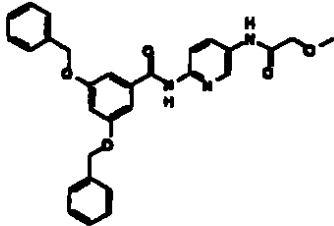
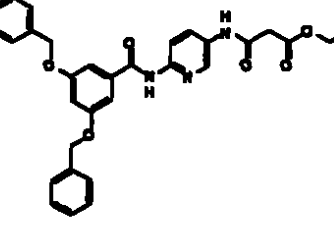
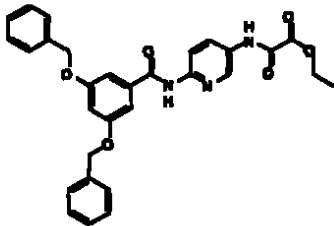
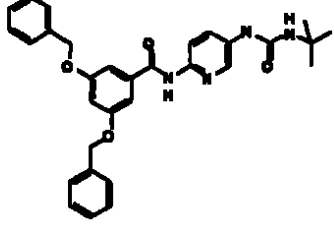
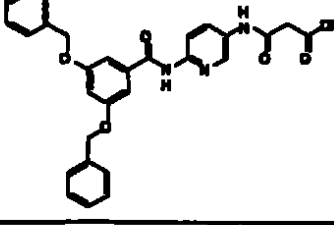
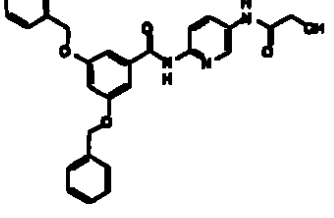


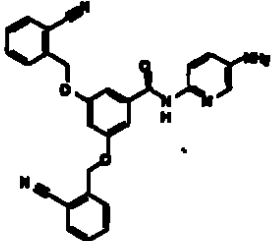
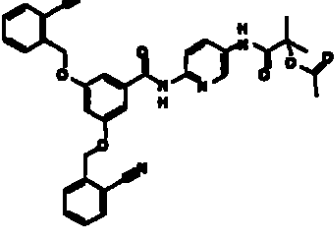
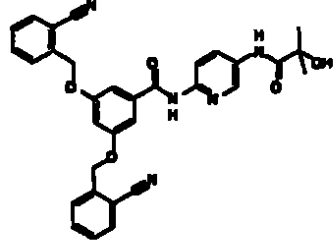
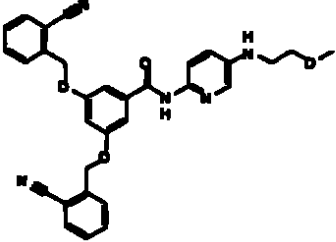
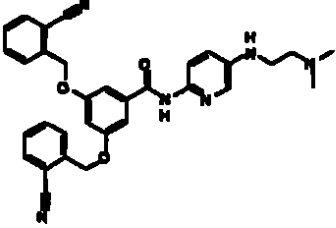
20 MH⁺ = 389, 391
M-H = 387, 389

EXAMPLE JJ:

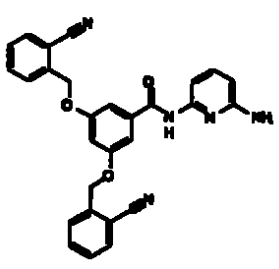
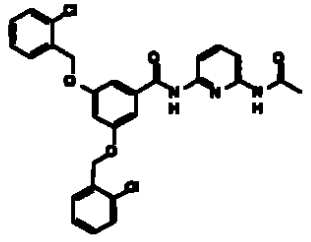
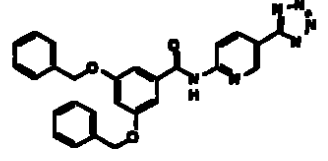
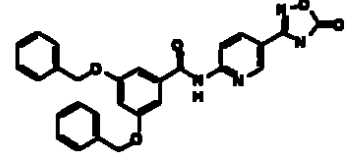
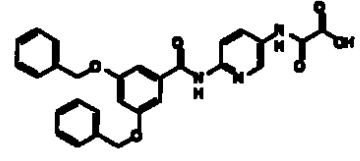
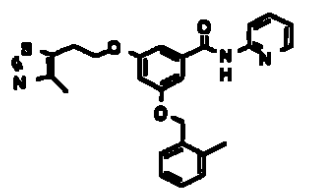
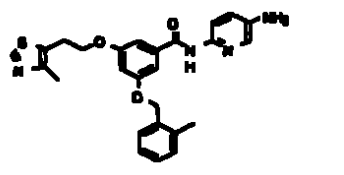
By analogous methods to those described above the following compounds, Example numbers JJ₁ to JJ₅₇, were also made.

Example	Structure	Route	LM-H ⁺	LM-H ⁺	NMR
1		7	426.19	424.25	1H NMR d (d6-DMSO): 5.17 (m, 6H), 6.80 (s, 1H), 7.00 (d, 1H), 7.26 to 7.46 (m, 12H), 7.71 (s, 1H), 7.78 (d, 1H), 10.28 (br s, 1H)
2		8		552.22	1H NMR d (d6-DMSO): 1.55 (s, 6H), 2.08 (s, 3H), 5.18 (s, 4H), 6.85 (s, 1H), 7.29 to 7.50 (m, 12H), 7.98 (dd, 1H), 8.13 (d, 1H), 8.61 (s, 1H), 9.70 (s, 1H), 10.72 (s, 1H)
3		9	512.16	510.22	1H NMR d (d6-DMSO): 1.35 (s, 6H), 5.18 (s, 4H), 6.88 (s, 1H), 7.28 to 7.48 (m, 12H), 8.08 (d, 1H), 8.22 (d, 1H), 8.82 (s, 1H), 9.90 (s, 1H), 10.96 (s, 1H)
4		8		502.49	1H NMR d (d6-DMSO): 3.02 (s, 3H), 5.17 (s, 4H), 6.86 (s, 1H), 7.29 to 7.58 (m, 12H), 7.70 (d, 1H), 8.13 (d, 1H), 8.24 (s, 1H), 9.83 (s, 1H), 10.83 (s, 1H)
5		8	526.41	524.45	1H NMR d (d6-DMSO): 2.13 (s, 3H), 4.65 (s, 2H), 5.18 (s, 4H), 6.84 (s, 1H), 7.27 to 7.48 (m, 12H), 7.96 (d, 1H), 8.13 (d, 1H), 8.61 (s, 1H), 10.24 (s, 1H), 10.73 (s, 1H)

Sample	Structure	Route	^1H NMR (d ₆ -DMSO)	^{13}C NMR (d ₆ -DMSO)	
6		8	498.55	496.55	^1H NMR d (d ₆ -DMSO): 3.39 (s, 3H), 4.01 (s, 1H), 5.18, (s, 4H), 6.85 (s, 1H), 7.28 to 7.50 (m, 12H), 8.07 (m, 2H), 8.67 (s, 1H), 9.95 (s, 1H), 10.71 (s, 1H)
7		8	540.58	538.63	^1H NMR d (d ₆ -DMSO): 1.20 (t, 3H), 3.47 (s, 2H), 4.11 (q, 2H), 5.17 (s, 4H), 6.83 (s, 1H), 7.28 to 7.48 (m, 12H), 7.95 (d, 1H), 8.13 (d, 1H), 8.60 (s, 1H), 10.35 (s, 1H), 10.73 (s, 1H)
8		8	526.53	524.61	^1H NMR d (d ₆ -DMSO): 1.30 (t, 3H), 4.30 (q, 2H), 5.17 (s, 4H), 6.86 (s, 1H), 7.28 to 7.50 (m, 12H), 8.14 (s, 2H), 8.74 (s, 1H), 10.78 (s, 1H), 10.97 (s, 1H)
9		10	525.61	523.66	^1H NMR d (d ₆ -DMSO): 1.30 (s, 9H), 5.18 (s, 4H), 6.09 (s, 1H), 6.85 (s, 1H), 7.32-7.50 (m, 12H), 7.78 (dd, 1H), 8.04 (d, 1H), 8.38 (s, 1H), 8.44 (s, 1H), 10.65 (s, 1H)
10		9	512.4		^1H NMR d (d ₆ -DMSO): 3.41 (s, 2H), 5.17 (s, 4H), 6.90 (s, 1H), 7.29 to 7.54 (m, 12H), 8.03 (d, 1H), 8.13 (d, 1H), 8.70 (s, 1H), 10.50 (s, 1H), 10.85 (s, 1H)
11		9	484.4		^1H NMR d (d ₆ -DMSO): 4.04 (s, 2H), 5.20 (s, 4H), 6.89 (s, 1H), 7.30 to 7.51 (m, 12 H), 8.12 (d, 1H), 8.22 (d, 1H), 8.81 (s, 1H), 10.05 (s, 1H), 11.00 (s, 1H)

Exemplar	Structure	Route	MW (H ₂ O)	MW (H ₂ O)	NMR
12		7	476.36		¹ H NMR d (d6-DMSO): 5.14 (s, 2H), 5.32 (s, 4H), 6.90 (s, 1H), 7.01 (dd, 1H), 7.35 (s, 2H), 7.59 (m, 2H), 7.80 (m, 6H), 7.90 (d, 2H), 10.38 (s, 1H) + 0.1 EtOAc
13		8	604.29	602.3	¹ H NMR d (d6-DMSO): 1.55 (s, 6H), 2.07 (s, 3H), 5.33 (s, 4H), 6.95 (s, 1H), 7.40 (s, 2H), 7.56 (m, 2H), 7.73 (m, 4H), 7.90 (d, 2H), 7.98 (dd, 1H), 8.13 (d, 1H), 8.63 (s, 1H), 9.71 (s, 1H), 10.82 (s, 1H)
14		9	562.28	560.27	¹ H NMR d (d6-DMSO): 1.34 (s, 6H), 5.32 (s, 4H), 6.97 (s, 1H), 7.40 (s, 2H), 7.57 (m, 2H), 7.75 (m, 4H), 7.90 (d, 2H), 8.09 (d, 1H), 8.21 (dd, 1H), 8.82 (s, 1H), 9.90 (s, 1H), 10.99 (s, 1H)
15		11	534.41		¹ H NMR d (d6-DMSO): 3.22 (t, 2H), 3.28 (t, 3H), 3.50 (t, 2H), 5.31 (s, 4H), 6.92 (s, 1H), 7.12 (dd, 1H), 7.34 (s, 2H), 7.57 (m, 2H), 7.75 (m, 5H), 7.82 (d, 1H), 7.91 (d, 2H), 10.49 (br s, 1H)
16		11	547.86		¹ H NMR d (d6-DMSO): 2.20 (s, 6H), 3.12 (m, 2H), 5.32 (s, 4H), 5.51 (br s, 1H), 6.89 (s, 1H), 7.06 (dd, 1H), 7.37 (s, 2H), 7.57 (m, 2H), 7.74 (m, 5H), 7.83 (d, 1H), 7.92 (d, 2H), 10.41 (s, 1H), and 2H under DMSO or water

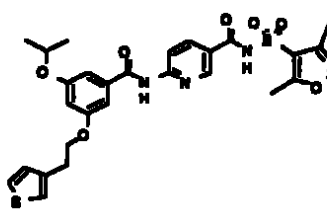
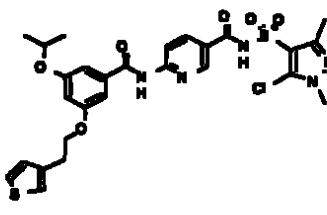
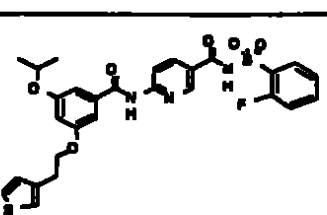
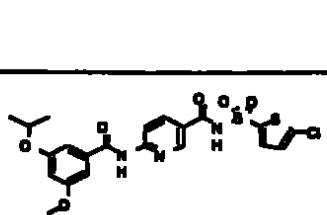
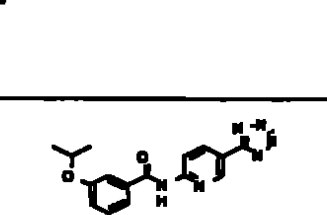
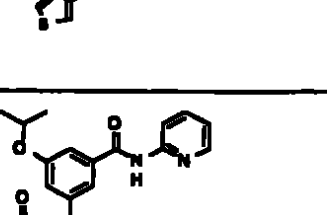
Ex. no	Structure	Yield (%)	¹ H NMR (d ₆ -DMSO)	Mass (m/z)	IR (cm ⁻¹)
17		11	504.54		1H NMR d (d ₆ -DMSO): 1.15 (t, 3H), 3.06 (quartet, 2H), 5.32 (s, 4H), 6.90 (s, 1H), 7.00 (dd, 1H), 7.35 (s, 2H), 7.57 (m, 2H), 7.73 (m, 5H), 7.85 (d, 1H), 7.92 (d, 2H), 10.41 (s, 1H)
18		12	485.5	483.5	1H NMR d (d ₆ -DMSO): 5.13 (s, 2H), 5.18 (s, 2H), 5.31 (s, 1H), 6.88 (s, 1H), 7.00 (dd, 1H), 7.32 (s, 2H), 7.40 (m, 3H), 7.50 (s, 1H), 7.58 (m, 1H), 7.74 (m, 3H), 7.80 (d, 1H), 7.90 (d, 1H), 10.33 (s, 1H)
19		1	493, 495		1H NMR d (d ₆ -DMSO): 2.35 (3H, s); 5.31 (4H, s); 6.98 (1H, t); 7.43-7.48 (6H, m); 7.58-7.61 (2H, m); 7.65-7.71 (3H, m); 8.14 (1H, d); 8.29 (1H, s); 10.84 (1H, s)
20		13	525		1H NMR d (d ₆ -DMSO): 3.10 (2H, m); 3.30 (6H, s); 3.60 (2H, m); 5.19 (4H, s); 6.89 (1H, s); 7.31-7.48 (12H, m); 8.29 (2H, m); 8.92 (1H, s); 11.05 (1H, s)
21		14	509		1H NMR d (d ₆ -DMSO): 4.5 (1H, d), 5.25 (s, 4H), 6.9 (s, 1H), 7.40 (m, 6H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (dd, 1H), 8.10 (d, 1H), 8.3 (s, 1H), 10.8 (br s, 1H);
22		1	494/496		1H NMR d (d ₆ -DMSO): 5.25 (4H, s); 5.65 (2H, s); 6.23 (1H, d); 6.85 (1H, s); 7.05-7.15 (3H, m); 7.18-7.22 (5H, m); 7.45-7.55 (2H, m); 7.58-7.62 (2H, m); 10.16 (1H, br s).

Ex. No.	Structure	Yield (%)	mp (°C)	1H NMR (d ₆ -DMSO)	
23		1	476	¹ H NMR d (d ₆ -DMSO): 5.25 (4H, s); 5.75 (2H, s); 6.22 (1H, d); 6.90 (1H, s); 7.25-7.41 (4H, m); 7.50-7.60 (2H, m); 7.70-7.80 (4H, m); 7.90 (2H, d); 10.19 (1H, br s).	
24		15	536/538	¹ H NMR d (d ₆ -DMSO): 3.25 (3H, s); 5.20 (4H, s); 6.9 (1H, t); 7.25 (2H, d); 7.35-7.40 (4H, m); 7.4 - 7.55 (2H, m); 7.58-7.63 (2H, m); 7.68-7.72 (1H, m); 7.75-7.80 (2H, d); 10.14 (1H, br s); 10.36 (1H, br s).	
25		16	479	477	¹ H NMR d (d ₆ -DMSO): 5.19 (4H, s); 6.88 (1H, s); 7.26-7.48 (12H, m); 8.40 (1H, d); 8.46 (1H, dd); 9.04 (1H, s); 11.13 (1H, br s).
26		17	495	493	¹ H NMR d (d ₆ -DMSO): 5.19 (4H, s); 6.87 (1H, s); 7.28-7.46 (12H, m); 8.21 (1H, dd); 8.38 (1H, d); 8.79 (1H, s); 11.14 (1H, br s).
27		18	498		¹ H NMR d (d ₆ -DMSO): 5.18 (4H, s); 6.88 (1H, s); 7.30-7.50 (12H, m); 8.17 (2H, s); 8.79 (1H, s); 10.79 (1H, s); 10.93 (1H, br s).
28		1	460		¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.36 (s, 3H), 3.23 (t, 2H), 4.22 (t, 2H), 5.13 (s, 2H), 6.78 (m, 1H), 7.11-7.24 (brm, 5H), 7.30 (m, 1H), 7.41 (d, 1H), 7.83 (m, 1H), 8.14 (d, 1H), 8.37 (m, 1H), 8.82 (s, 1H), 10.74 (brs, 1H).
29		7	475		¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.36 (s, 3H), 3.22 (t, 2H), 4.20 (t, 2H), 5.11 (s, 4H), 6.72 (m, 1H), 7.00 (m, 1H), 7.15-7.28 (brm, 5H), 7.41 (d, 1H), 7.73 (m, 2H), 8.82 (s, 1H), 10.29 (brs, 1H).

Sample	Structure	Route	MW	Yield	NMR
30		1			¹ H NMR δ (d ₆ -DMSO): 2.66 (s, 3H), 5.15 (s, 4H), 6.88 (m, 1H), 7.14 (m, 1H), 7.39-7.47 (brn, 7H), 7.52 (s, 1H), 7.83 (m, 1H), 8.15 (d, 1H), 8.38 (m, 1H), 10.72 (brs, 1H).
31		1b	395		
32		1			¹ H NMR δ (d ₆ -DMSO): 1.28 (d, 6H), 2.39 (s, 3H), 4.72 (m, 1H), 5.20 (s, 2H), 6.33 (s, 1H), 6.72 (s, 1H), 7.14 (m, 1H), 7.20 (s, 1H), 7.27 (s, 1H), 7.82 (m, 1H), 8.13 (d, 1H), 8.36 (d, 1H), 10.72 (brs, 1H).
33		1			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 4.71 (m, 1H), 5.21 (s, 2H), 6.73 (t, 1H), 7.12 - 7.29 (brn, 5H), 7.22 (m, 1H), 7.56 (m, 1H), 7.83 (m, 1H), 8.14 (d, 1H), 8.35 (m, 1H), 10.72 (brs, 1H).
34		1b	311		
35		1b	451		
36		1b	398		
37		1	374	372	¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 2.01 (m, 1H), 3.60 (d, 2H), 4.71 (m, 1H), 6.67 (ap t, 1H), 7.17 (ap d, 2H), 8.39 (d, 1H), 8.63 (dd, 1H), 9.20 (d, 1H), 11.43 (bs, 1H)
38		7b	344		¹ H NMR δ (d ₆ -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.00 (m, 1H), 3.78 (d, 2H), 4.69 (m, 1H), 5.12 (s, 2H), 6.58 (t, 1H), 6.99 (dd, 1H), 7.1 (ap d, 2H), 7.73-7.78 (m, 2H), 10.24 (bs, 1H)

Example	Structure	Empirical Formula	MW	MS	¹ H NMR
39		C ₂₄ H ₃₀ N ₂ O ₄	386		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.26 (d, 6H), 2.01 (m, 1H), 2.05 (s, 3H), 3.79 (d, 2H), 4.70 (m, 1H), 6.61 (ap t, 1H), 7.14 (ap d, 2H), 7.95 (dd, 1H), 8.08 (d, 1H), 7.59 (ap d, 1H), 10.07 (bs, 1H)
40		C ₂₄ H ₃₀ N ₂ O ₄	422	420	¹ H NMR δ (d ₆ -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.03 (m, 1H), 3.01 (s, 3H), 3.79 (d, 2H), 4.70 (m, 1H), 6.63 (ap t, 1H), 7.14 (ap d, 2H), 7.70 (dd, 1H), 8.12 (d, 1H), 8.34 (ap d, 1H), (9.83, s, 1H), 10.81 (bs, 1H)
41		C ₂₄ H ₃₀ N ₂ O ₄	M+H 430 M-H 428		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 1.35 (s, 6H), 2.01 (m, 1H), 3.79 (d, 2H), 4.70 (m, 1H), 5.71 (s, 1H), 6.61 (s, 1H), 7.15 (s, 2H), 8.06-8.15 (m, 2H), 8.76 (ap d, 1H), 9.78 (s, 1H), 10.65 (bs, 1H)
42		C ₂₄ H ₃₀ N ₂ O ₄	412 (M+HCO OH) ⁺ 456		¹ H NMR δ (d ₆ -DMSO): 0.79-0.82 (m, 4H), 0.98 (d, 6H), 1.26 (d, 6H), 1.77 (m, 1H), 2.01 (m, 1H), 4.70 (h, 1H), 6.11 (ap t, 1H), 7.14 (ap d, 2H), 7.95 (dd, 1H), 8.08 (d, 1H), 8.62 (ap d, 1H), 10.33 (bs, 1H), 10.64 (bs, 1H)
43		C ₂₄ H ₃₀ N ₂ O ₄	450 M+H 450 M-H 448		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 2.01 (m, 1H), 3.37 (s, 3H), 3.80 (d, 2H), 4.71 (m, 1H), 6.65 (ap t, 1H), 7.17 (s, 2H), 8.27-8.35 (m, 2H), 8.91 (m, 1H), 11.13 (bs, 1H)
44		C ₂₄ H ₃₀ N ₂ O ₄	1c 352		δ _H (300MHz, DMSO-d ₆) 0.94-1.02 (6H,d); 1.24-1.34 (6H,d); 1.095-2.10 (1H,m); 3.76-3.84 (2H,d); 4.64-4.77 (1H,m); 6.64-6.70 (1H,m); 7.14-7.17 (2H,m); 8.25-8.36 (2H,m); 8.85 (1H,m); 11.21 (1H,s)
45		C ₂₄ H ₃₀ N ₂ O ₄	8 (a) 7c		δ _H (300MHz, DMSO-d ₆) 0.94-1.03 (6H,d); 1.26-1.30 (6H,d); 1.95-2.08 (1H,m); 2.90 (3H,s); 3.75-3.84 (2H,d); 4.04-4.26 (2H,d + H ₂ O); 4.65-4.77 (1H,m); 6.64 (1H,m); 7.15 (2H,m); 7.50-7.62 (1H,broad t); 7.80-7.90 (1H,d of m); 8.08-8.16 (1H,app d); 8.35 (1H, m); 10.84 (1H,m)

Example	Structure	Name	MW	Yield	NMR
46		8 (a) 7c			δ_H (300MHz, DMSO- d_6) 0.94-1.02 (6H, d); 1.24-1.30 (6H, d); 1.84 (3H, s); 1.95-2.07 (1H, m); 3.75-3.83 (2H, d); 4.18-4.27 (2H, d); 4.64-4.76 (1H, m); 6.62 (1H, m); 7.15 (2H, m); 7.63-7.73 (1H, app d of m); 8.05-8.13 (1H, app d); 8.27 (1H, s); 8.30-8.38 (1H, app broad t); 10.69 (1H, s)
46a		1a	408	406	δ_H (300MHz, DMSO- d_6) 1.26 (d, 6H), 3.05 (t, 2H), 4.25 (t, 2H), 4.72 (sept, 1H), 6.68 (s, 1H), 7.12 (d, 1H), 7.16 (s, 1H), 7.19 (s, 1H), 7.33 (s, 1H), 7.47 (dd, 1H), 8.30 (m, 2H), 8.83 (s, 1H), 11.23 (bs, 1H)
47		27	504		δ_H (300MHz, DMSO- d_6) 1.27 (d, 6H), 3.06 (t, 2H), 3.38 (s, 3H), 4.25 (t, 2H), 4.71 (sept, 1H), 6.68 (t, 1H), 7.11 (dd, 1H), 7.12 (s, 1H), 7.17 (s, 1H), 7.31 (d, 1H), 7.46 (dd, 1H), 8.29 (d, 1H), 8.34 (dd, 1H), 8.92 (d, 1H), 11.14 (bs, 1H)
48		27	584	582	δ_H (300MHz, DMSO- d_6) 1.25 (d, 6H), 3.04 (t, 2H), 4.23 (t, 2H), 4.69 (sept, 1H), 6.67 (s, 1H), 7.11 (d, 1H), 7.15 (s, 1H), 7.20 (s, 1H), 7.31 (d, 1H), 7.46 (m, 3H), 8.07 (dd, 2H), 8.26 (s, 2H), 8.86 (s, 1H), 11.13 (bs, 1H)
49		27	556		δ_H (300MHz, DMSO- d_6) 1.27 (d, 6H), 3.04 (t, 2H), 4.23 (t, 2H), 4.71 (sept, 1H), 6.64 (s, 1H), 7.11 (d, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.32 (s, 1H), 7.46 (dd, 1H), 8.19 (m, 2H), 8.82 (d, 1H), 10.93 (bs, 1H)
50		27	567		δ_H (300MHz, DMSO- d_6) 1.26 (d, 6H), 3.04 (t, 2H), 4.24 (t, 2H), 4.70 (sept, 1H), 6.64 (t, 1H), 7.11 (dd, 1H), 7.16 (s, 1H), 7.21 (s, 1H), 7.30 (m, 1H), 7.46 (m, 1H), 8.16 (m, 3H), 8.62 (d, 1H), 8.83 (s, 1H), 8.98 (s, 1H), 10.90 (bs, 1H)

Example	Structure	Route	¹ H-NMR	¹³ C-NMR	IR
51		27	585	583	δ_H (300MHz, DMSO-d ₆) 1.27 (d, 6H), 2.39 (s, 3H), 2.68 (s, 3H), 3.06 (t, 2H), 4.26 (t, 2H), 4.73 (sept, 1H), 6.69 (t, 1H), 7.12 (d, 1H), 7.17 (s, 1H), 7.22 (s, 1H), 7.33 (m, 1H), 7.49 (m, 1H), 8.28 (m, 2H), 8.89 (s, 1H), 11.10 (bs, 1H)
52		27	618/620 (1xCl)	616/618 (1xCl)	δ_H (300MHz, DMSO-d ₆) 1.28 (d, 6H), 2.40 (s, 3H), 3.08 (t, 2H), 3.79 (s, 3H), 4.25 (t, 2H), 4.71 (sept, 1H), 6.68 (s, 1H), 7.12 (d, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.34 (m, 1H), 7.39 (s, 1H), 7.48 (dd, 1H), 8.30 (m, 2H), 8.92 (s, 1H), 11.15 (bs, 1H)
53		27	584		δ_H (300MHz, DMSO-d ₆) 1.26 (d, 6H), 3.04 (t, 2H), 4.24 (t, 2H), 4.70 (sept, 1H), 6.66 (t, 1H), 7.12 (dd, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.30 (m, 1H), 7.37 (m, 1H), 7.45 (dd, 1H), 7.67 (m, 1H), 7.78 (dt, 1H), 7.96 (dt, 1H), 8.822 (s, 2H), 8.86 (s, 1H), 11.08 (bs, 1H)
54		27	606	604	δ_H (300MHz, DMSO-d ₆) 1.26 (d, 6H), 3.04 (t, 2H), 4.25 (t, 2H), 4.71 (sept, 1H), 6.64 (t, 1H), 7.00 (d, 1H), 7.12 (dd, 1H), 7.16 (s, 1H), 7.22 (s, 1H), 7.32 (m, 2H), 7.46 (dd, 1H), 8.14 (d, 1H), 8.22 (dd, 1H), 8.83 (t, 1H), 10.87 (bs, 1H)
55		16	451	449	δ_H (300MHz, DMSO-d ₆) 1.28 (d, 6H), 3.06 (t, 2H), 4.26 (t, 2H), 4.72 (sept, 1H), 6.65 (s, 1H), 7.12 (d, 1H), 7.18 (s, 1H), 7.23 (s, 1H), 7.32 (s, 1H), 7.47 (m, 1H), 8.23 (d, 1H), 8.32 (dd, 1H), 8.95 (s, 1H), 10.81 (bs, 1H)
56		1a	329.48	327.46	

57		1a	354.46	352.43	
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Notes:

* Final products prepared by hydrolysis method 2a; requisite starting materials prepared according to generic alkylation methodology followed by coupling (Route 1).

5 ** Final products prepared by reductive amination method 6 method ; requisite starting materials prepared according to generic alkylation methodology followed by coupling (Route 1) and hydrolysis (Route 2a).

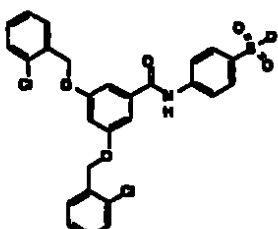
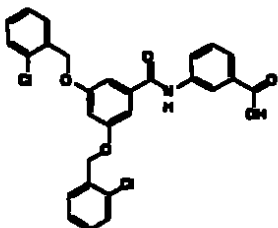
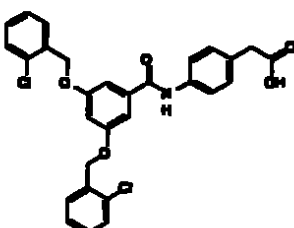
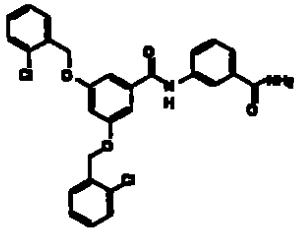
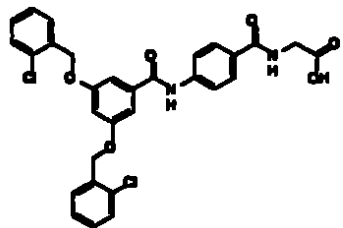
*** Final products prepared by hydrolysis (Route 2a) or acid chloride coupling (Route 1); requisite starting materials prepared according to generic alkylation methodology followed by coupling (Route 1).

EXAMPLE KK:

By analogous methods to those described above the following compounds, Example numbers KK₁ to KK₇, were also made.

15

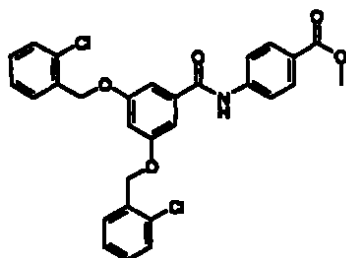
Example	Structure	Route	(MW)	(MW)	¹ H NMR (CDCl ₃)
1		2b *	522	520	¹ H NMR d (d6-DMSO): 5.20 (4H, s); 6.95 (1H, s); 7.25 (2H, s); 7.30-7.5 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 7.8 - 8.0 (4H, s).
2		1	494		No data

Example	Structure	Route	Yield (%)	mp (°C)	1H NMR (d6-DMSO)
3		1		556/558	NMR not right
4		2b	522		1H NMR d (d6-DMSO): 5.25 (4H, s); 6.95 (1H, s); 7.25 (2H, s); 7.35-7.55 (7H, m); 7.6 - 7.7 (3H, m); 8.05 (1H, d); 8.4 (1H, s); 10.3 (1H, br s); 12.9 (1H, br s).
5		2b *	536	534	1H NMR d (d6-DMSO): 3.4 (2H, s); 5.2 (4H, s); 6.95 (1H, s); 7.2 (4H, m); 7.4 (4H, m); 7.5 (2H, m); 7.6 - 7.7 (4H, m); 10.1 (1H, br s).
6		1		519	1H NMR d (d6-DMSO): 5.2 (4H, s); 6.95 (1H, m); 7.25 (2H, m); 7.4 (5H, m); 7.5 (2H, m); 7.55 - 7.65 (4H, m); 7.9 (2H, m); 8.2 (1H, s); 10.3 (1H, br s).
7		1		577	V. poor spectrum

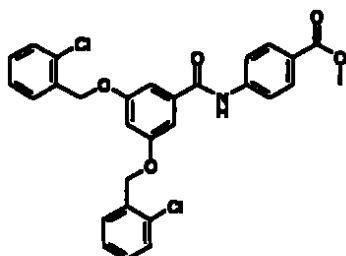
* For Examples KK₁ and KK₅, the ester intermediates were prepared by route 1:

70

16



¹H NMR δ (d₆-DMSO): 3.8 (3H, s); 5.25 (4H, s); 6.95 (1H, t); 7.25 (2H, d); 7.4 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 8.0 (4H, q); 10.6 (1H, br s).



5

¹H NMR δ (d₆-DMSO): 1.2 (3H, t); 3.6 (2H, s); 4.1 (2H, q); 5.25 (4H, s); 6.95 (1H, t); 7.2 (4H, m); 7.4 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 7.7 (2H, m); 10.15 (1H, br s).

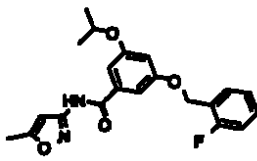
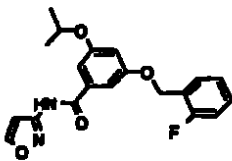
EXAMPLE LL:

10 By analogous methods to those described above the following compounds, Example numbers LL₁ to LL₃, were also made.

Ex. no.	Structure	Formula	Mp (°C)	M _w	NMR
1		1a	360		
2		1a	382		
3		1a	412		

EXAMPLE MM:

By analogous methods to those described above the following compounds, Example numbers MM₁ to MM₂, were also made.

Example	Structure	Formula	MW	MP	NMR
1		1a	385		
2		1a	371		

BIOLOGICAL

Tests:

The biological effects of the compounds of formula (I) or (IA) or (IB) may be tested in the following way:

(1) Enzymatic activity of GLK may be measured by incubating GLK, ATP and glucose. The rate of product formation may be determined by coupling the assay to a G-6-P dehydrogenase, NADP/NADPH system and measuring the increase in optical density at 340nm (Matschinsky et al 1993).

(2) A GLK/GLKRP binding assay for measuring the binding interactions between GLK and GLKRP. The method may be used to identify compounds which modulate GLK by modulating the interaction between GLK and GLKRP. GLKRP and GLK are incubated with an inhibitory concentration of F-6-P, optionally in the presence of test compound, and the extent of interaction between GLK and GLKRP is measured. Compounds which either displace F-6-P or in some other way reduce the GLK/GLKRP interaction will be detected by a decrease in the amount of GLK/GLKRP complex formed. Compounds which promote F-6-P binding or in some other way enhance the GLK/GLKRP interaction will be detected by an

increase in the amount of GLK/GLKRP complex formed. A specific example of such a binding assay is described below

GLK/GLKRP scintillation proximity assay

- 5 The compounds A to S (described in Examples A to S) and 1 to 118 (described in Examples T to Y) were found to have an activity of at least 40% activity at 10 μ m when tested in the GLK/GLKRP scintillation proximity assay described below.

Recombinant human GLK and GLKRP were used to develop a "mix and measure" 96 well SPA (scintillation proximity assay) as described in WO01/20327 (the contents of which are incorporated herein by reference). GLK (Biotinylated) and GLKRP are incubated with streptavidin linked SPA beads (Amersham) in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P (Amersham Custom Synthesis TRQ8689), giving a signal. Compounds which either displace the F-6-P or in some other way disrupt the GLK / GLKRP binding interaction will cause this signal to be lost.

Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, recombinant biotinylated GLK (0.1 mg), recombinant GLKRP (0.1 mg), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of GLK/GLKRP complex formation was determined by addition of 0.1mg/well avidin linked SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

(3) A F-6-P / GLKRP binding assay for measuring the binding interaction between GLKRP and F-6-P. This method may be used to provide further information on the mechanism of action of the compounds. Compounds identified in the GLK/GLKRP binding assay may modulate the interaction of GLK and GLKRP either by displacing F-6-P or by modifying the GLK/GLKRP interaction in some other way. For example, protein-protein interactions are generally known to occur by interactions through multiple binding sites. It is thus possible that a compound which modifies the interaction between GLK and GLKRP could act by binding to one or more of several different binding sites.

The F-6-P / GLKRP binding assay identifies only those compounds which modulate the interaction of GLK and GLKRP by displacing F-6-P from its binding site on GLKRP.

GLKRP is incubated with test compound and an inhibitory concentration of F-6-P, in the absence of GLK, and the extent of interaction between F-6-P and GLKRP is measured. Compounds which displace the binding of F-6-P to GLKRP may be detected by a change in the amount of GLKRP/F-6-P complex formed. A specific example of such a binding assay is described below

F-6-P / GLKRP scintillation proximity assay

Recombinant human GLKRP was used to develop a "mix and measure" 96 well scintillation proximity assay) as described in WO01/20327 (the contents of which are incorporated herein by reference). FLAG-tagged GLKRP is incubated with protein A coated SPA beads (Amersham) and an anti-FLAG antibody in the presence of an inhibitory concentration of radiolabelled [3H]F-6-P. A signal is generated. Compounds which displace the F-6-P will cause this signal to be lost. A combination of this assay and the GLK/GLKRP binding assay will allow the observer to identify compounds which disrupt the GLK/GLKRP binding interaction by displacing F-6-P.

Binding assays were performed at room temperature for 2 hours. The reaction mixtures contained 50mM Tris-HCl (pH 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, recombinant FLAG tagged GLKRP (0.1 mg), Anti-Flag M2 Antibody (0.2mg) (IBI Kodak), 0.05mCi [3H] F-6-P (Amersham) to give a final volume of 100ml. Following incubation, the extent of F-6-P/GLKRP complex formation was determined by addition of 0.1mg/well protein A linked SPA beads (Amersham) and scintillation counting on a Packard TopCount NXT.

Production of recombinant GLK and GLKRP:

25 *Preparation of mRNA*

Human liver total mRNA was prepared by polytron homogenisation in 4M guanidine isothiocyanate, 2.5mM citrate, 0.5% Sarkosyl, 100mM b-mercaptoethanol, followed by centrifugation through 5.7M CsCl, 25mM sodium acetate at 135,000g (max) as described in Sambrook J, Fritsch EF & Maniatis T, 1989.

30 Poly A⁺ mRNA was prepared directly using a FastTrack™ mRNA isolation kit (Invitrogen).

72
M

PCR amplification of GLK and GLKRP cDNA sequences

Human GLK and GLKRP cDNA was obtained by PCR from human hepatic mRNA using established techniques described in Sambrook, Fritsch & Maniatis, 1989. PCR primers were designed according to the GLK and GLKRP cDNA sequences shown in Tanizawa et al 1991 and Bonthron, D.T. *et al* 1994 (later corrected in Warner, J.P. 1995).

Cloning in Bluescript II vectors

GLK and GLKRP cDNA was cloned in *E. coli* using pBluescript II, (Short et al 1998) a recombinant cloning vector system similar to that employed by Yanisch-Perron C *et al* (1985), comprising a *colEI*-based replicon bearing a polylinker DNA fragment containing multiple unique restriction sites, flanked by bacteriophage T3 and T7 promoter sequences; a filamentous phage origin of replication and an ampicillin drug resistance marker gene.

Transformations

E. Coli transformations were generally carried out by electroporation. 400 ml cultures of strains DH5a or BL21(DE3) were grown in L-broth to an OD 600 of 0.5 and harvested by centrifugation at 2,000g. The cells were washed twice in ice-cold deionised water, resuspended in 1ml 10% glycerol and stored in aliquots at -70°C. Ligation mixes were desalted using Millipore V series™ membranes (0.0025mm) pore size). 40ml of cells were incubated with 1ml of ligation mix or plasmid DNA on ice for 10 minutes in 0.2cm electroporation cuvettes, and then pulsed using a Gene Pulser™ apparatus (BioRad) at 0.5kVcm⁻¹, 250mF, 250 Ω. Transformants were selected on L-agar supplemented with tetracycline at 10mg/ml or ampicillin at 100mg/ml.

Expression

GLK was expressed from the vector pTB375NBSE in *E.coli* BL21 cells, producing a recombinant protein containing a 6-His tag immediately adjacent to the N-terminal methionine. Alternatively, another suitable vector is pET21(+)DNA, Novagen, Cat number 697703. The 6-His tag was used to allow purification of the recombinant protein on a column packed with nickel-nitrilotriacetic acid agarose purchased from Qiagen (cat no 30250).

GLKRP was expressed from the vector pFLAG CTC (IBI Kodak) in *E.coli* BL21 cells, producing a recombinant protein containing a C-terminal FLAG tag. The protein was purified

initially by DEAE Sepharose ion exchange followed by utilisation of the FLAG tag for final purification on an M2 anti-FLAG immunoaffinity column purchased from Sigma-Aldrich (cat no. A1205).

5 Biotinylation of GLK:

GLK was biotinylated by reaction with biotinamidocaproate N-hydroxysuccinimide ester (biotin-NHS) purchased from Sigma-Aldrich (cat no. B2643). Briefly, free amino groups of the target protein (GLK) are reacted with biotin-NHS at a defined molar ratio forming stable amide bonds resulting in a product containing covalently bound biotin. Excess, non-
10 conjugated biotin-NHS is removed from the product by dialysis. Specifically, 7.5mg of GLK was added to 0.31mg of biotin-NHS in 4mL of 25mM HEPES pH7.3, 0.15M KCl, 1mM dithiothreitol, 1mM EDTA, 1mM MgCl₂ (buffer A). This reaction mixture was dialysed against 100mL of buffer A containing a further 22mg of biotin-NHS. After 4hours excess biotin-NHS was removed by extensive dialysis against buffer A.

15

PHARMACEUTICAL COMPOSITIONS

The following illustrate representative pharmaceutical dosage forms of the invention as
20 defined herein (the active ingredient being termed "Compound X"), for therapeutic or prophylactic use in humans:

25	(a)	<u>Tablet I</u>	<u>mg/tablet</u>
		Compound X.....	100
		Lactose Ph.Eur.....	182.75
		Croscarmellose sodium.....	12.0
		Maize starch paste (5% w/v paste).....	2.25
		Magnesium stearate.....	3.0
30	(b)	<u>Tablet II</u>	<u>mg/tablet</u>
		Compound X.....	50
		Lactose Ph.Eur.....	223.75
		Croscarmellose sodium.....	6.0

Xy/33

Maize starch.....	15.0
Polyvinylpyrrolidone (5% w/v paste).....	2.25
Magnesium stearate.....	3.0

5	(c)	<u>Tablet III</u>	<u>mg/tablet</u>
		Compound X.....	1.0
		Lactose Ph.Eur.....	93.25
		Croscarmellose sodium.....	4.0
		Maize starch paste (5% w/v paste).....	0.75
10		Magnesium stearate.....	1.0
	(d)	<u>Capsule</u>	<u>mg/capsule</u>
		Compound X.....	10
		Lactose Ph.Eur.....	488.5
15		Magnesium.....	1.5
	(e)	<u>Injection I</u>	<u>(50 mg/ml)</u>
		Compound X.....	5.0% w/v
		1M Sodium hydroxide solution.....	15.0% v/v
20		0.1M Hydrochloric acid (to adjust pH to 7.6)	
		Polyethylene glycol 400.....	4.5% w/v
		Water for injection to 100%	
	(f)	<u>Injection II</u>	<u>(10 mg/ml)</u>
25		Compound X.....	1.0% w/v
		Sodium phosphate BP.....	3.6% w/v
		0.1M Sodium hydroxide solution.....	15.0% v/v
		Water for injection to 100%	
30	(g)	<u>Injection III</u>	<u>(1mg/ml, buffered to pH6)</u>
		Compound X.....	0.1% w/v
		Sodium phosphate BP.....	2.26% w/v
		Citric acid.....	0.38% w/v

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Polyethylene glycol 400..... 3.5% w/v
Water for injection to 100%

(h)	<u>Aerosol I</u>	<u>mg/ml</u>
5	Compound X.....	10.0
	Sorbitan trioleate.....	13.5
	Trichlorofluoromethane.....	910.0
	Dichlorodifluoromethane.....	490.0
10	(i) <u>Aerosol II</u>	<u>mg/ml</u>
	Compound X.....	0.2
	Sorbitan trioleate.....	0.27
	Trichlorofluoromethane.....	70.0
	Dichlorodifluoromethane.....	280.0
15	Dichlorotetrafluoroethane.....	1094.0
	(j) <u>Aerosol III</u>	<u>mg/ml</u>
	Compound X.....	2.5
	Sorbitan trioleate.....	3.38
20	Trichlorofluoromethane.....	67.5
	Dichlorodifluoromethane.....	1086.0
	Dichlorotetrafluoroethane.....	191.6
	(k) <u>Aerosol IV</u>	<u>mg/ml</u>
25	Compound X.....	2.5
	Soya lecithin.....	2.7
	Trichlorofluoromethane.....	67.5
	Dichlorodifluoromethane.....	1086.0
	Dichlorotetrafluoroethane.....	191.6
30	(l) <u>Ointment</u>	<u>ml</u>
	Compound X.....	40 mg
	Ethanol.....	300 µl

Water.....	300 µl
1-Dodecylazacycloheptan-2-one.....	50 µl
Propylene glycol.....	to 1 ml

5 Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate. The aerosol formulations (h)-(k) may be used in conjunction with standard, metered dose aerosol

10 dispensers, and the suspending agents sorbitan trioleate and soya lecithin may be replaced by an alternative suspending agent such as sorbitan monooleate, sorbitan sesquioleate, polysorbate 80, polyglycerol oleate or oleic acid.

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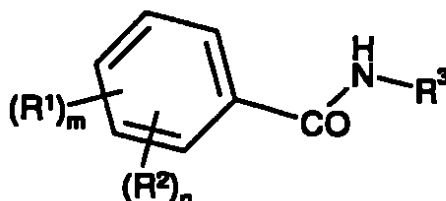
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CLAIMS:

1. The use of a compound of Formula (I) or a salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the treatment or prevention of a disease or
 5 medical condition mediated through GLK:



Formula (I)

wherein

- m is 0, 1 or 2;
 10 n is 0, 1, 2, 3 or 4;
 and $n + m > 0$;
 each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_2-CH_2F$, $-(CH_2)_{1-4}CH_2-CH_2F$,
 $-OCH_2-CH_2F$, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, NH_2 , $-NH-C_{1-4}$ alkyl,
 $-N$ -di- $(C_{1-4}$ alkyl), CN, formyl, phenyl or heterocyclyl optionally substituted by
 15 C_{1-6} alkyl;
 each R^2 is the group $Y-X$ -
 wherein each X is a linker independently selected from:
 $-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$,
 $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-(CH_2)_{1-4}-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$,
 20 $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$, $-Z-$,
 $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z-$, $-O-Z-N(R^6)-Z-$, $-O-C(O)-Z-O-Z-$ or a
 direct bond;
 each Z is independently a direct bond, C_{2-6} alkenylene or a group of the formula
 $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$;
 25 each Y is independently selected from aryl- Z^1- , heterocyclyl- Z^1- ,
 C_{3-7} cycloalkyl- Z^1- , C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_{1-4}CH_2-CH_2F$ or
 $-CH(OH)CH_2-CH_2F$; wherein each Y is independently optionally substituted by up
 to 3 R^4 groups;

each R^4 is independently selected from halo, $-\text{CH}_2\text{F}$, CN , NH_2 , $\text{C}_{1-6}\text{alkyl}$,
 $-\text{OC}_{1-6}\text{alkyl}$, $-\text{COOH}$, $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$, OH or phenyl optionally
substituted by $\text{C}_{1-6}\text{alkyl}$ or $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$,
or $\text{R}^5\text{-X}^1$ -, where X^1 is independently as defined in X above and R^5 is
5 selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$, $-\text{CH}_2\text{F}$, phenyl, naphthyl,
heterocyclyl or $\text{C}_{3-7}\text{cycloalkyl}$; and R^5 is optionally substituted by one or
more substituents independently selected from: halo, $\text{C}_{1-6}\text{alkyl}$,
 $-\text{OC}_{1-6}\text{alkyl}$, $-\text{CH}_2\text{F}$, CN , OH , NH_2 , COOH , or $-\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$,
each Z^1 is independently a direct bond, $\text{C}_{2-6}\text{alkenylene}$ or a group of the
10 formula $-(\text{CH}_2)_p\text{-C}(\text{R}^{6a})_2\text{-(CH}_2)_q$;

R^3 is selected from phenyl or a heterocyclyl, and R^3 is optionally substituted by one
or more R^7 groups;

R^6 is independently selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$ or $-\text{C}_{2-4}\text{alkyl-O-C}_{1-4}\text{alkyl}$;

R^{6a} is independently selected from hydrogen, halo, $\text{C}_{1-6}\text{alkyl}$ or
15 $-\text{C}_{2-4}\text{alkyl-O-C}_{1-4}\text{alkyl}$;

each R^7 is independently selected from:

$\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$, $\text{C}_{2-6}\text{alkynyl}$, $(\text{CH}_2)_{0-3}\text{aryl}$, $(\text{CH}_2)_{0-3}\text{heterocyclyl}$,
 $(\text{CH}_2)_{0-3}\text{C}_{3-7}\text{cycloalkyl}$, OH , $\text{C}_{1-6}\text{alkyl-OH}$, halo, $\text{C}_{1-6}\text{alkyl-halo}$, $\text{OC}_{1-6}\text{alkyl}$,
 $(\text{CH}_2)_{0-3}\text{S}(\text{O})_{0-2}\text{R}^8$, SH , SO_3 , thioxo, NH_2 , CN , $(\text{CH}_2)_{0-3}\text{NHSO}_2\text{R}^8$,
20 $(\text{CH}_2)_{0-3}\text{COOH}$, $(\text{CH}_2)_{0-3}\text{-O-(CH}_2)_{0-3}\text{R}^8$, $(\text{CH}_2)_{0-3}\text{C}(\text{O})(\text{CH}_2)_{0-3}\text{R}^8$,
 $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^8$, $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NH}_2$, $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NH}(\text{CH}_2)_{0-3}\text{R}^8$,
 $(\text{CH}_2)_{0-3}\text{NH}(\text{CH}_2)_{0-3}\text{R}^8$, $(\text{CH}_2)_{0-3}\text{NHC}(\text{O})(\text{CH}_2)_{0-3}\text{R}^8$; $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NHSO}_2\text{-R}^8$ and
 $(\text{CH}_2)_{0-3}\text{SO}_2\text{NHC}(\text{O})\text{-R}^8$ wherein an alkyl chain, cycloalkyl ring or heterocyclyl
ring within R^7 is optionally substituted by one of more substituents independently
25 selected from: $\text{C}_{1-4}\text{alkyl}$, OH , halo, CN , NH_2 , $\text{N-C}_{1-4}\text{alkylamino}$,
 $\text{N,N-di-C}_{1-4}\text{alkylamino}$ and $\text{OC}_{1-4}\text{alkyl}$;

R^8 is selected from hydrogen, $\text{C}_{1-6}\text{alkyl}$, aryl, heterocyclyl, $\text{C}_{3-7}\text{cycloalkyl}$, OH ,
 $\text{C}_{1-6}\text{alkyl-OH}$, COOH , $\text{C}(\text{O})\text{OC}_{1-6}\text{alkyl}$, $\text{N}(\text{R}^6)\text{C}_{1-6}\text{alkyl}$, $\text{OC}_{1-6}\text{alkyl}$,
 $\text{C}_{0-6}\text{alkylOC}(\text{O})\text{C}_{1-6}\text{alkyl}$, $\text{C}(\text{OH})(\text{C}_{1-6}\text{alkyl})\text{C}_{1-6}\text{alkyl}$; wherein an alkyl chain or
30 aryl, heterocyclyl or cycloalkyl ring within R^8 is optionally substituted by one of
more substituents independently selected from: $\text{C}_{1-4}\text{alkyl}$, OH , halo, CN , NH_2 ,
 $-\text{NH-C}_{1-4}\text{alkyl}$, $-\text{N-di-(C}_{1-4}\text{alkyl)}$ and $\text{OC}_{1-4}\text{alkyl}$;

each a is independently 1, 2 or 3;

p is an integer between 0 and 3;

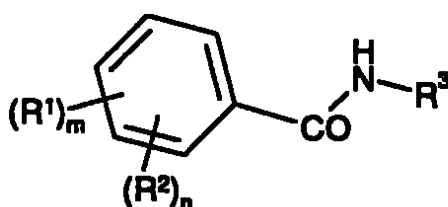
q is an integer between 0 and 3;

and $p + q < 4$.

- 5 provided that when R^3 is 2-pyridyl and X is other than $-Z-$, $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z-$ or $-O-Z-N(R^6)-Z-$, then R^3 cannot be mono-substituted at the 5-position with an R^7 group selected from $COOH$ or $C(O)OC_{1-6}alkyl$.

- 10 2. A pharmaceutical composition comprising a compound of Formula (I) as claimed in claim 1, or a salt, solvate or pro-drug thereof, together with a pharmaceutically-acceptable diluent or carrier for use in the preparation of a medicament for use in the treatment or prevention of a disease or medical condition mediated through GLK.

3. A compound of Formula (Ib) or a salt, solvate or pro-drug thereof



Formula (Ib)

wherein

m is 0, 1 or 2;

n is 1, 2 or 3;

- 20 and $n + m$ is 2 or 3;

each R^1 is independently selected from OH , $-(CH_2)_{1-4}OH$, $-CH_2F$, $-(CH_2)_{1-4}CH_2F$, $-OCH_2F$, halo, OCH_3 , C_2H_5O , $CH_3C(O)O-$, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-NH-C_{1-4}alkyl$, $-N-di-(C_{1-4}alkyl)$, CN , formyl, phenyl or heterocyclyl optionally substituted by $C_{1-6}alkyl$;

- 25 each R^2 is the group $Y-X-$

with the proviso that $Y-X-$ cannot be CH_3O , C_2H_5O or $CH_3C(O)O-$;

wherein each X is a linker independently selected from:

$-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$,

-CON(R⁶)-Z-, -C(O)N(R⁶)S(O)₂-Z-, -S(O)₂N(R⁶)C(O)-Z-, -C(O)-Z-, -Z-,
-C(O)-Z-O-Z-, -N(R⁶)-C(O)-Z-O-Z-, -O-Z-N(R⁶)-Z-, -O-C(O)-Z-O-Z- or a
direct bond except where Z is C₁₋₆alkyl;

each Z is independently a direct bond, C₂₋₆alkenylene or a group of the formula

5 -(CH₂)_p-C(R^{6a})₂-(CH₂)_q;

each Y is independently selected from aryl-Z¹-, heterocyclyl-Z¹-,

C₃₋₇cycloalkyl-Z¹-, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, -(CH₂)₁₋₄CH₃₋₃F₃ or
-CH(OH)CH₃₋₃F₃; wherein each Y is independently optionally substituted by
up to 3 R⁴ groups;

10 each R⁴ is independently selected from halo, -CH₃₋₃F₃, CN, NH₂, C₁₋₄alkyl,
-OC₁₋₆alkyl, -COOH, -C(O)OC₁₋₆alkyl, OH or phenyl optionally
substituted by C₁₋₆alkyl or -C(O)OC₁₋₆alkyl,
or R⁵-X¹-, where X¹ is independently as defined in X above and R⁵ is
selected from hydrogen, C₁₋₆alkyl, -CH₃₋₃F₃, phenyl, naphthyl,
15 heterocyclyl or C₃₋₇cycloalkyl; and R⁵ is optionally substituted by one
or more substituents independently selected from: halo, C₁₋₆alkyl,
-OC₁₋₆alkyl, -CH₃₋₃F₃, CN, OH, NH₂, COOH, or -C(O)OC₁₋₆alkyl,
each Z¹ is independently a direct bond, C₂₋₆alkenylene or a group of
the formula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q;

20 R³ is heterocyclyl, wherein the atom at the two position of the heterocyclyl ring
relative to the amide group, to which R³ is attached, is a heteroatom and when the
atom at the two position of the heterocyclyl ring relative to the amide group is
nitrogen, this is an sp² hybridised nitrogen, and R³ is optionally substituted by up
to 2 R⁷ groups;

25 R⁶ is independently selected from hydrogen, C₁₋₆alkyl or -C₂₋₄alkyl-O-C₁₋₄alkyl;

R^{6a} is independently selected from hydrogen, halo, C₁₋₆alkyl or
-C₂₋₄alkyl-O-C₁₋₄alkyl;

each R⁷ is independently selected from:

30 C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, (CH₂)₀₋₃aryl, (CH₂)₀₋₃heterocyclyl,
(CH₂)₀₋₃C₃₋₇cycloalkyl, OH, C₁₋₆alkyl-OH, halo, C₁₋₆alkyl-halo, OC₁₋₆alkyl,
(CH₂)₀₋₃S(O)₀₋₂R⁸, SH, SO₃, thioxo, NH₂, CN, (CH₂)₀₋₃NHSO₂R⁸,
(CH₂)₀₋₃COOH, (CH₂)₀₋₃-O-(CH₂)₀₋₃R⁸, (CH₂)₀₋₃C(O)(CH₂)₀₋₃R⁸,

$(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^8$, $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NH}_2$, $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NH}(\text{CH}_2)_{0-3}\text{R}^8$,
 $(\text{CH}_2)_{0-3}\text{NH}(\text{CH}_2)_{0-3}\text{R}^8$, $(\text{CH}_2)_{0-3}\text{NHC}(\text{O})(\text{CH}_2)_{0-3}\text{R}^8$; $(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{NHSO}_2\text{-R}^8$ and
 $(\text{CH}_2)_{0-3}\text{SO}_2\text{NHC}(\text{O})\text{-R}^8$ wherein an alkyl chain, cycloalkyl ring or heterocyclyl
 ring within R^7 is optionally substituted by one of more substituents independently
 5 selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 , N-C_{1-4} alkylamino,

N,N-di-C_{1-4} alkylamino and OC_{1-4} alkyl;

R^8 is selected from hydrogen, C_{1-6} alkyl, aryl, heterocyclyl, C_{3-7} cycloalkyl, OH,

C_{1-6} alkyl-OH, COOH, $\text{C}(\text{O})\text{OC}_{1-6}$ alkyl, $\text{N}(\text{R}^6)\text{C}_{1-6}$ alkyl, OC_{1-6} alkyl,

C_{0-6} alkyl $\text{OC}(\text{O})\text{C}_{1-6}$ alkyl, $\text{C}(\text{OH})(\text{C}_{1-6}\text{alkyl})\text{C}_{1-6}$ alkyl; wherein an alkyl chain or

10 aryl, heterocyclyl or cycloalkyl ring within R^8 is optionally substituted by one of
 more substituents independently selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 ,
 $-\text{NH-C}_{1-4}$ alkyl, $-\text{N-di-(C}_{1-4}\text{alkyl)}$ and OC_{1-4} alkyl;

each a is independently 1, 2 or 3;

p is an integer between 0 and 3;

15 q is an integer between 0 and 3;

and $p + q < 4$.

provided that

(i) when R^3 is 2-pyridyl and X is other than $-\text{Z}-$, $-\text{C}(\text{O})\text{-Z-O-Z-}$, $-\text{N}(\text{R}^6)\text{-C}(\text{O})\text{-Z-O-Z-}$
 or $-\text{O-Z-N}(\text{R}^6)\text{-Z-}$, then R^3 cannot be mono-substituted at the 5-position with an
 20 R^7 group selected from COOH or $\text{C}(\text{O})\text{OC}_{1-6}$ alkyl;

(ii) positions 3,5 on the phenyl ring (to which R^1 and R^2 are attached) relative to the
 amide bond are substituted and at least one of the groups at position 3 and 5 is an
 R^2 group;

(iii) an unbranched, unsubstituted C_{1-6} alkyl chain cannot exceed C_6 alkyl in length;

25 (iv) when n is 2 or 3 then only one X group can be $-\text{NHC}(\text{O})\text{-}$;

(v) when R^3 is pyridyl and R^7 is halo or methyl then the phenyl ring to which R^2 is
 attached cannot be substituted by an R^2 group at the 2-position relative to the
 amide bond wherein X is $-\text{C}(\text{O})\text{NH-}$ and Y is optionally substituted phenyl,
 optionally substituted thienyl or optionally substituted pyridyl;

30 (vi) when $n+m$ is 2, m is 0 or m is 1 and R^1 is OH, n is 1 and X is $-\text{NHC}(\text{O})\text{-}$ or n is 2
 and X is independently selected from $-\text{C}(\text{O})\text{NH-}$, $-\text{NHC}(\text{O})\text{-}$, $-\text{O-}$, $-\text{S}(\text{O}_2)\text{NH-}$ or
 a direct bond wherein one X group is $-\text{NHC}(\text{O})\text{-}$, Y is selected from phenyl,

cyclohexyl, 4,5-dihydro-5-oxo-pyrazolyl, thienyl,

1,3-dihydro-1,3-dioxo-isoindolyl, 2-oxo-1-benzopyran or pyridyl and Y is optionally substituted by R⁴ then R³ cannot be unsubstituted thiazole,

4,5-dihydro-5-oxo-pyrazolyl substituted by trichlorophenyl,

- 5 4,5,6,7-tetrahydro-benzo[b]thiophene substituted by ethoxycarbonyl or pyridyl optionally independently mono or di-substituted by methyl, ethoxy or propylcarbonylamino; and

- (vii) when n+m is 3, m is 0 or 2, R¹ is independently selected from methyl, methoxy or hydroxy, n is 1, 2 or 3, X is independently selected from -O-, -S(O₂)NH-,
10 -C(O)-, -S(O₂)-, -CH₂- or a direct bond, Y is selected from pyrrolidinyl, morpholino, phenyl, tetrazolyl or propyl wherein Y is optionally substituted by R⁴ and R⁴ is selected from di-hydroxy, methoxy, C₁₋₄alkyl then R³ cannot be unsubstituted tetrazolyl, unsubstituted thiazolyl or thiazolyl substituted by ethoxycarbonylmethyl.

15

4. A compound according to claim 3, or salt, solvate or pro-drug thereof, wherein each R¹ is independently selected from OH, formyl, CH₃-F₂, OCH₃-F₂, halo, C₁₋₆alkyl, NH₂, CN, (CH₂)₁₋₄OH or a heterocyclyl optionally substituted by C₁₋₆alkyl.

- 20 5. A compound according to claim 3 or claim 4, or salt, solvate or pro-drug thereof, wherein each R² is the group Y-X-, each X is independently selected from -Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -OC(O)-Z-, -C(O)-Z-O-Z-, -O-C(O)-Z-O-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R⁶)-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z-, -N(R⁶)-C(O)-Z-O-Z-, -SO₂N(R⁶)-Z-, -N(R⁶)SO₂-Z- or -O-Z-N(R⁶)-Z-, each Y is
25 independently selected from C₁₋₆alkyl, C₂₋₆alkenyl, aryl-Z¹-, heterocyclyl-Z¹-, C₃₋₇cycloalkyl(CH₂)₀₋₂-, -(CH₂)₁₋₄CH₃-F₂ and each Y is independently optionally substituted by R⁴.

6. A compound according to any one of claims 3 to 5, or salt, solvate or pro-drug thereof,
30 wherein each R⁴ is independently selected from halo, CH₃-F₂, OCH₃-F₂, CN, C₁₋₆alkyl, OC₁₋₆alkyl, COOH, C(O)OC₁₋₆alkyl, (CH₂)₀₋₃COOH, O(CH₂)₀₋₃COOH, CO-phenyl, CONH₂, CONH-phenyl, SO₂NH₂, SO₂C₁₋₆alkyl, OH, or phenyl optionally substituted by

one or more R^5 groups where R^5 is selected from hydrogen, C_{1-6} alkyl or $C(O)OC_{1-6}$ alkyl.

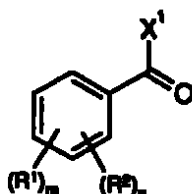
7. A compound according to any one of claims 3 to 6, or salt, solvate or pro-drug thereof,
5 wherein R^3 is a nitrogen-containing heterocyclyl, optionally substituted by one or more R^7 groups.
8. A compound according to claim 7, or a salt, solvate or prodrug thereof, wherein R^3 is
10 selected from thiazole, benzothiazole, thiadiazole, pyridine, pyrazine, pyridazine, pyrazole, imidazole, pyrimidine, oxazole and indole.
9. A compound according to any one of claims 3 to 8, or salt, solvate or pro-drug thereof,
wherein R^3 is unsubstituted or is substituted by one R^7 group.
- 15 10. A compound according to any one of claims 3 to 9, or salt, solvate or pro-drug thereof,
wherein each R^7 is independently selected from OH, CN, NH_2 , SO_3 , thioxo, halo, C_{1-4} alkyl, C_{1-4} alkyl-OH, O- C_{1-4} alkyl, C_{1-4} alkyl-halo, $(CH_2)_{0-1}COOH$, $(CH_2)_{0-1}C(O)OR^8$,
 $(CH_2)_{0-1}NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}NHC(O)(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$,
20 $-(CH_2)_{0-2}S(O)_{0-2}R^8$, $-(CH_2)_{0-1}N(R^6)SO_2R^8$, $(CH_2)_{0-1}C(O)N(R^6)S(O)_2R^8$ or
 $(CH_2)_{0-1}$ heterocyclyl.
11. A compound according to any one of claims 3 to 10, or salt, solvate or pro-drug thereof,
wherein Y is phenyl- Z^1 - optionally substituted by halo or C_{1-6} alkyl.
- 25 12. A compound according to any one of claims 3 to 11, or salt, solvate or pro-drug thereof,
wherein each R^2 is the group Y-X-, Z within the definition of X is a direct bond and Z^1
within the definition of Y is a group of the formula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$.
13. A pharmaceutical composition comprising a compound according to any one of claims 3
30 to 12, or a salt, solvate or prodrug thereof, together with a pharmaceutically-acceptable
diluent or carrier.

14. The use of a compounds of Formula (I), as defined in claim 1, or a salt, solvate or pro-drug thereof, in the preparation of a medicament for use in the combined treatment or prevention of diabetes and obesity.

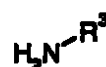
5 15. The use of a compound of Formula (Ib) or a salt, pro-drug or solvate thereof, as defined in claim 3, as a medicament.

16. A process for the preparation of a compound of Formula (I), or salt, solate or pro-drug thereof, as defined in claim 1, which comprises:

10 (a) reaction of a compound of Formula (IIIa) with a compound of Formula (IIIb),



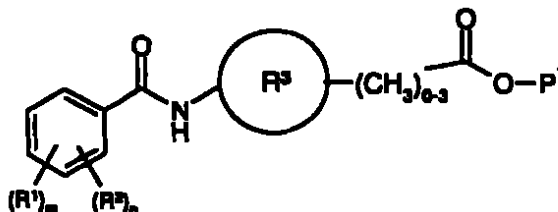
Formula (IIIa)



Formula (IIIb); or

wherein X¹ is a leaving group

15 (b) for compounds of Formula (I) wherein R³ is hydrogen, de-protection of a compound of Formula (IIIc),



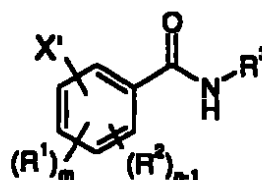
Formula (IIIc)

wherein P¹ is a protecting group;

20 (c) for compounds of Formula (I) wherein n is 1, 2, 3 or 4, reaction of a compound of Formula (IIIId) with a compound of Formula (IIIe),



Formula (IIIId)



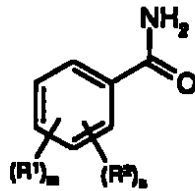
Formula (IIIe)

wherein X¹ and X'' comprises groups which when reacted together form the group X;

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(d) for a compound of Formula (I) wherein n is 1, 2, 3 or 4 and X or X¹ is -SO-Z- or -SO₂-Z-, oxidation of the corresponding compound of Formula (I) wherein X or X¹ respectively is -S-Z-;

(e) reaction of a compound of Formula (III_f) with a compound of Formula (III_g),

Formula (III_f)Formula (III_g)

wherein X² is a leaving group;

and thereafter, if necessary:

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

ii) removing any protecting groups;

iii) forming a salt, pro-drug or solvate thereof.

PATENT COOPERATION TREATY

93.344

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:		CODE		DATE		NT		NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT	
BRYANT, Tracey ASTRAZENECA Global Intellectual Property Merreside, Alderley Park Macclesfield Cheshire SK10 4TG GRANDE BRETAGNE		ANKOM		08 JUN 2003		GPS		(PCT Rule 71.1)	
		DATA ENTERED		Date of mailing (day/month/year)		03/06/2003			
Applicant's or agent's file reference 100379/WO		FINAL CHECK						IMPORTANT NOTIFICATION	
International application No. PCT/GB 02/03745			International filing date (day/month/year) 15/08/2002			Priority date (day/month/year) 17/08/2001			
Applicant ASTRAZENECA AB et al.									

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPRA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

LODOLO F
Tel. (+49-89) 2399 2828



PATENT C OPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference 100379/WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 02/ 03745	International filing date (day/month/year) 15/08/2002	Priority date (day/month/year) 17/08/2001
International Patent Classification (IPC) or national classification and IPC A61K31/425		
Applicant ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 18/02/2003	Date of completion of this report 28/05/2003
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epro d Fax: (+49-89) 2399-4465	Authorized officer TZSCHOPPE D A Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/GB 02/03745

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I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

(12) SOLICITUD INTERNACIONAL PUBLICADA SEGÚN EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

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27 de febrero de 2003 (27.02.2003)

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(71) Solicitante (para todos los países destinatarios con excepción de MG, US): ASTRAZENECA AB [SE/SE]; Sodertälje, S-161 85 (SE).

(71) Solicitante (para MG únicamente): ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London, Greater London W1Y 6LN (GB).

(72) Inventores, e

(75) Inventores/Solicitantes (para US únicamente): BOYD, Scott [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). CAULKETT, Peter, William, Rodney [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). HARGREAVES, Rodney, Brian [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). BOWKER, Suzanna, Saxon [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JAMES, Roger [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). JOHNSTONE, Craig [GB/GB]; Alderley

Park, Macclesfield, Cheshire SK10 4TG (GB). JONES, Clifford, David [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). MCKERRECHER, Darren [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). BLOCK, Michael, Howard [GB/US]; 35 Gatehouse Drive, Waltham, MA 02451 (US).

(74) Agentes: BRYANT, Tracey, et al.; AstraZeneca, Global Intellectual Property, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB)

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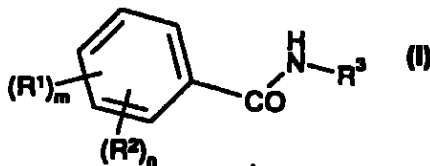
(84) Países destinatarios (regional): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Eursiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente Europea (AT, BE, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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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: COMPUESTOS QUE AFECTAN LA GLUCOCINASA



(57) Extracto: La invención se refiere al uso de un compuesto de Fórmula (I) o una sal, solvato o profármaco del mismo, en donde R^1 , R^2 , R^3 , n y m son como se describe en la especificación, en la preparación de un medicamento para el tratamiento o prevención de una condición de enfermedad mediada por glucocinasa (GLK), tal como diabetes tipo 2. La invención se relaciona asimismo con un grupo novedoso de compuestos de Fórmula (I) y con métodos para preparar compuestos de Fórmula (I).

WO 03/015774 A1



COMPUESTOS QUE AFECTAN LA GLUCOCINASA

La presente invención se refiere al uso de un grupo de compuestos de benzamida en la preparación de un medicamento para uso en el tratamiento o prevención de una enfermedad o condición médica mediada por glucocinasa (GLK), que lleva a un umbral disminuido de glucosa para secreción de insulina. Se afirma, además, que los compuestos bajan la glucosa sanguínea aumentando la absorción de glucosa hepática. Tales compuestos pueden tener utilidad en el tratamiento de la diabetes tipo 2 y la obesidad. La invención concierne asimismo a composiciones farmacéuticas que comprenden dicho compuesto de benzamida, un subgrupo de compuestos novedosos de dichos compuestos de benzamida, y el uso de dicho compuesto en las condiciones descritas anteriormente.

En las células β del páncreas y en las células parenquimales del hígado el principal transportador de glucosa de la membrana plasmática es GLUT2. Bajo concentraciones fisiológicas de glucosa la velocidad a la cual GLUT2 transporta glucosa a través de la membrana no es limitante de la velocidad con respecto a la velocidad total de absorción de glucosa en estas células. La velocidad de la absorción de glucosa está limitada por la velocidad de fosforilación de la glucosa al glucosa-6-fosfato (G-6-P), que se cataliza por la glucocinasa (GLK) [1]. La GLK tiene una elevada K_m (6-10mM) para la glucosa y no está inhibida por concentraciones fisiológicas de G-6-P [1]. La expresión de GLK está limitada unos pocos tejidos y tipos de células, muy notablemente las células β del páncreas y las células del hígado (hepatocitos) [1]. En estas células la actividad GLK es limitante de la velocidad para la utilización de glucosa y, por lo tanto, regula el grado de secreción de insulina inducida por glucosa y la síntesis hepática de glucógeno. Estos procesos son críticos en el mantenimiento de la homeostasis de la glucosa en todo el organismo y los dos son disfuncionales en la diabetes [2].

En un sub-tipo de diabetes, la diabetes de inicio en la edad madura de los jóvenes (MODY-2), la diabetes es causada por la pérdida GLK de

mutaciones funcionales [3, 4]. La hiperglicemia en pacientes MODY-2 resulta de una deficiente utilización de la glucosa a la vez en el páncreas y en el hígado [5]. La utilización deficiente de la glucosa en el páncreas de pacientes MODY-2 resulta en un umbral elevado de secreción de insulina inducida por la glucosa. Inversamente, mutaciones activadoras, poco frecuentes, de GLK reducen este umbral con el resultado de un hiperinsulinismo familiar [6, 7]. Además de la reducida actividad GLK observada en diabéticos MODY-2, la actividad de la glucocinasa hepática se disminuye también en diabéticos tipo 2 [8]. En forma digna de consideración, la sobre-expresión global o selectivo del hígado de la GLK evita o reversa el desarrollo del fenotipo diabético tanto en los modelos alimenticios como genéticos de la enfermedad [9-12]. Más aún, el tratamiento inmediato 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 es mediado por un aumento inducido por la fructosa en la actividad GLK citosólica en el hepatocito por el mecanismo descrito más adelante [13].

La actividad GLK hepática está inhibida por la asociación con la proteína reguladora GLK (GLKRP). El complejo GLK/GLKRP se estabiliza por la unión del fructosa-6-fosfato (F6P) a la GLKRP y se desestabiliza por el desplazamiento de este fosfato de azúcar por el fructosa-1-fosfato (F1P). F1P se genera por fosforilación mediada por fructocinasa de la fructosa alimenticia. Consecuentemente, la integridad del complejo GLK/GLKRP y la actividad GLK hepática se regulan en una forma dependiente de la nutrición ya que F6P se eleva en el estado post-absorbente mientras que F1P predomina en el estado post-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 está regulada exclusivamente por la disponibilidad de su sustrato, la glucosa. Pequeñas moléculas pueden activar la GLK directamente o a través de la desestabilización del complejo GLK/GLKRP. Se afirma que la anterior clase de compuestos estimulan la utilización de glucosa tanto en el hígado

como en el páncreas, mientras se afirma que los últimos actúan exclusivamente en el hígado. No obstante, se afirma que compuestos con cualquiera de los dos perfiles tienen una ventaja terapéutica en el tratamiento de la diabetes tipo 2 puesto que esta enfermedad se caracteriza por la utilización deficiente de glucosa en ambos tejidos.

GLK y GLKRP y el canal K_{ATP} se expresan en las neuronas del hipotálamo, una región del cerebro que es importante en la regulación del balance de energía y el control de la ingesta de alimento [14-18]. Se ha demostrado que estas neuronas expresan neuropéptidos orexígenos y anorexígenos [15, 19, 20] y se ha asumido que son las neuronas que detectan la glucosa en el hipotálamo las que son inhibidas o excitadas por cambios en concentraciones de glucosa ambiente [17, 19, 21, 22]. La capacidad de estas neuronas de detectar cambios en los niveles de glucosa es deficiente en una variedad de modelos, genéticos e inducidos experimentalmente, 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 alimentación [31]. Por consiguiente, los activadores de pequeñas moléculas de GLK pueden disminuir la ingesta de alimentos y el aumento de peso a través de efectos centrales sobre la GLK. Por lo tanto, los activadores de GLK pueden tener uso terapéutico en el tratamiento de desórdenes en la alimentación, 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 en normalizar la homeostasis de la glucosa, para el tratamiento de la diabetes tipo 2. Así, el sistema GLK/GLKRP puede describirse como una Diana potencial de "diabesidad" (de utilidad tanto en la diabetes como la obesidad).

En WO0058293 y WO01/44216 (Roche), una serie de compuestos de benzilcarbamoilo se describen 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 ensayo en el cual la

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actividad GLK se asocia a la producción de NADH, la que a su vez se mide ópticamente – ver detalles del ensayo *in vitro* descrito en Ejemplo A. Los compuestos de la presente invención pueden activar la GLK directamente o pueden activar la GLK inhibiendo la interacción de GLKRP con GLK. El último mecanismo ofrece una importante ventaja sobre los activadores directos de la GLK en que ellos no causarán los episodios hipoglicémicos severos predichos después de la estimulación directa. Muchos compuestos de la presente invención pueden mostrar una selectividad favorable comparada con activadores conocidos de GLK.

WO9622282, WO9622293, WO9622294, WO9622295, WO9749707 y WO9749708 divulgan un número de intermedios usados en la preparación de compuestos útiles como agentes de vasopresina los cuales son estructuralmente similares a los divulgados en la presente invención. Compuestos estructuralmente similares se divulgan asimismo en WO9641795 y JP8143565 (antagonismo de vasopresina), en JP8301760 (prevención del daño de la piel) y en EP619116 (osteopatía).

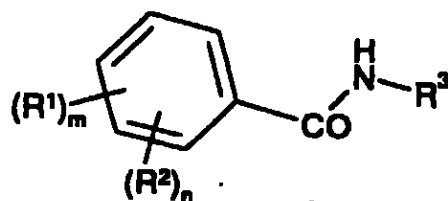
WO01/12621 describe la preparación de isoxazolilpirimidinas y compuestos relacionados como inhibidores de cinasas cJUN N-terminales, y composiciones farmacéuticas que contienen dichos compuestos.

Cushman y *colegas* [Bioorg Med Chem Lett (1991) 1(4). 211-14] describen la síntesis de estilbenos con contenido de piridina y amidas y su evaluación como inhibidores de protein-tirosin cinasa. Rogers y *colegas* [J Med Chem (1981) 24(11) 1284-7] describen análogos de purinona mesoiónica como inhibidores de AMP fosfodiesterasa cíclica.

WO00/26202 describe la preparación de derivados de 2-amino-tiazol como agentes antitumorales. GB 2331748 describe la preparación de derivados insecticidas de tiazol. WO96/36619 describe la preparación de derivados de aminotiazol como agentes para mejorar los movimientos del tracto digestivo. US 5466715 y US5258407 describen la preparación de inmunoestimulantes de fenol 3,4-disustituido. JP 58069812 describe productos farmacéuticos hipoglicémicos que contienen derivados de benzamida. US 3950351 describe 2-benzamido-5-nitrotiazoles y Cavier y

colegas [Eur J Med Chem - Chim Ther (1978) 13(6), 539-431 discuten el interés biológico de estos compuestos.

Presentamos como característica de la invención el uso de un compuesto de Fórmula (I) o una sal, solvato o profármaco del mismo, en la preparación de un medicamento para uso en el tratamiento o prevención de una enfermedad o condición médica mediada por GLK:



Fórmula (I)

en donde

m es 0, 1 ó 2;

n es 0, 1, 2, 3 ó 4;

cada **R¹** se selecciona independientemente de OH, $-(CH_2)_{1-4}OH$, $-CH_2F$, $-(CH_2)_{1-4}CH_2F$, $-OCH_2F$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, NH_2 , $-NH-C_{1-4}$ alquilo, $-N-di-(C_{1-4}$ alquil), CN, formilo, fenilo o heterociclilo sustituido opcionalmente por C_{1-6} alquilo;

cada **R²** es el grupo **Y-X-**

en donde cada **X** es un enlazante seleccionado independientemente de:

$-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$, $-Z-$, $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z-$, $-O-Z-N(R^6)-Z-$, $-O-C(O)-Z-O-Z-$ o un enlace directo;

cada **Z** es independientemente un enlace directo, C_{2-6} alquenileno o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$;

cada **Y** se selecciona independientemente de aril-**Z¹**-, heterociclil-**Z¹**-,

C_{3-7} cicloalquil- Z^1 -, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, -
(CH_2)₁₋₄ CH_3 - F_n o -CH(OH) CH_3 - F_n ; en donde cada Y se
sustituye independientemente en forma opcional por hasta 3
grupos R^4 ;

cada R^4 se selecciona independientemente de halo, - CH_3 - F_n ,
CN, NH_2 , C_{1-6} alquilo, - OC_{1-6} alquilo, -COOH, -
C(O) OC_{1-6} alquilo, OH o fenil sustituido opcionalmente
por C_{1-6} alquilo o -C(O) OC_{1-6} alquilo, o R^5 - X^1 -, donde X^1
es independientemente como se define en X más arriba
y R^5 se selecciona de hidrógeno. C_{1-6} alquilo, - CH_3 - F_n ,
fenilo, naftilo, heterociclilo o C_{3-7} cicloalquilo; y R^5 se
sustituye opcionalmente por uno o más sustituyentes
seleccionados independientemente de: halo, C_{1-6} alquilo,
 OC_{1-6} alquilo, - CH_3 - F_n , CN, OH, NH_2 , COOH, o -
C(O) OC_{1-6} alquilo,

cada Z^1 es independientemente un enlace directo, C_{2-6}
alquenileno o un grupo de la fórmula -(CH_2)_p-C(R^{6a})₂-
(CH_2)_q;

R^3 se selecciona de fenilo o un heterociclilo, y R^3 se sustituye
opcionalmente por uno o más grupos R^7 ;

R^6 se selecciona independientemente de hidrógeno, C_{1-6} alquilo o - C_{2-6}
alquil-O- C_{1-4} alquilo;

R^{6a} se selecciona independientemente de hidrógeno, halo, C_{1-6} alquilo o - C_{2-6}
alquil-O- C_{1-4} alquilo;

cada R^7 se selecciona independientemente de:

C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, (CH_2)₀₋₃arilo, (CH_2)₀₋₃heterociclilo, (CH_2)₀₋₃ C_{3-7} cicloalquilo, OH, C_{1-6} alquilo, OH, halo,
 C_{1-6} alquil-halo, OC_{1-6} alquilo, (CH_2)₀₋₃S(O)₀₋₂ R^8 , SH, SO₃, tioxo,
 NH_2 , CN, (CH_2)₀₋₃NHSO₂ R^8 , (CH_2)₀₋₃COOH, (CH_2)₀₋₃-O-(CH_2)₀₋₃ R^8 ,
(CH_2)₀₋₃C(O)(CH_2)₀₋₃ R^8 , (CH_2)₀₋₃C(O)OR⁸, (CH_2)₀₋₃C(O) NH_2 ,
(CH_2)₀₋₃C(O)NH(CH_2)₀₋₃ R^8 , (CH_2)₀₋₃NH(CH_2)₀₋₃ R^8 , (CH_2)₀₋₃NHC(O)(CH_2)₀₋₃ R^8 ;
(CH_2)₀₋₃C(O)NHSO₂- R^8 y (CH_2)₀₋

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$_3\text{SO}_2\text{NHC(O)-R}^8$ en donde una cadena alquilo, anillo cicloalquilo o anillo heterociclilo dentro de R^7 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, $-\text{OH}$, halo, CN , NH_2 , N-C_{1-4} alquilamino, N,N-di-C_{1-4} alquilamino y OC_{1-4} alquilo;

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, arilo, heterociclilo, C_{3-7} cicloalquilo, OH , C_{1-6} alquil- OH , COOH , C(O)OC_{1-6} alquilo, $\text{N(R}^6\text{)C}_{1-6}$ alquilo, OC_{1-6} alquilo, C_{0-6} alquil OC(O)C_{1-6} alquilo, $\text{C(OH)(C}_{1-6}\text{alquil)C}_{1-6}$ alquilo; en donde una cadena alquilo o arilo, heterociclilo o anillo cicloalquilo dentro de R^8 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, OH , halo, CN , NH_2 , $-\text{NH-C}_{1-4}$ alquilo, $-\text{N-di-(C}_{1-4}\text{alquil)}$ y OC_{1-4} alquilo,

cada a es independientemente 1, 2 ó 3;

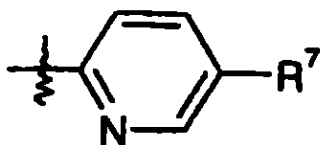
p es un entero entre 0 y 3;

q es un entero entre 0 y 3;

y $p + q < 4$.

con la condición que cuando R^3 es 2-piridilo y X es distinto a $-\text{Z}-$, $-\text{C(O)-Z-O-Z-}$, $-\text{N(R}^6\text{)-C(O)-Z-O-Z-}$ ó $-\text{O-Z-N(R}^6\text{)-Z-}$, entonces R^3 no puede ser mono-sustituido en la posición 5- con un grupo R^7 seleccionado de COOH ó C(O)OC_{1-6} alquilo.

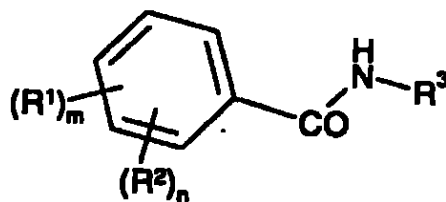
Para evitar dudas, la numeración en la condición anterior es relativa al enlace amida unido al anillo de piridina; por consiguiente R^3 en la condición anterior se refiere a un grupo de la siguiente estructura:



en donde  representa el punto de unión al grupo amida en Fórmula (I).

De acuerdo con una característica adicional de la invención se provee el uso de un compuesto de Fórmula (Ia) o una sal del mismo, en la

preparación de un medicamento para uso en el tratamiento o prevención de una enfermedad o condición médica mediada por GLK:



Fórmula (Ia)

en donde

m es 0, 1 ó 2;

n es 0, 1, 2, 3 ó 4;

y $n + m > 0$;

cada R^1 se selecciona independientemente de OH, $(CH_2)_{1-4}OH$, CH_3-F_n , $(CH_2)_{1-4}CH_3-F_n$, OCH_3-F_n , halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, NH_2 , $N(C_{1-6}alquil)C_{1-6}alquilo$, CN, fenilo o un heterociclilo sustituido opcionalmente por C_{1-6} alquilo;

cada R^2 es el grupo Y-X-

en donde cada X es un enlazante seleccionado independientemente de

$-O(CH_2)_{0-3}-$, $-(CH_2)_{0-3}O-$, $-C(O)O(CH_2)_{0-3}-$, $-S(CH_2)_{0-3}-$, $-SO(CH_2)_{0-3}-$, $-SO_2(CH_2)_{0-3}-$, $-NHSO_2-$, $-SO_2NH-$, $-N(CH_2)_{0-3}-$, $-N(CH_2)_{1-3}O(CH_2)_{0-3}-$, $-(CH_2)_{1-4}-$, $-CH=CH(CH_2)_{0-2}-$, $-C\equiv C(CH_2)_{0-2}-$, $-NHCO-$, $-CONH-$;

cada Y se selecciona independientemente de fenil $(CH_2)_{0-2}$, naftil $(CH_2)_{0-2}$, heterociclil $(CH_2)_{0-2}$, C_{3-7} cicloalquil $(CH_2)_{0-2}$, C_{1-6} alquilo, OC_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, o $CH(OH)CH_3-F_n$;

cada Y es independientemente sustituido opcionalmente por uno o más grupos R^4 ;

cada R^4 se selecciona independientemente de halo, CH_3-F_n , OCH_3-F_n , CN, NH_2 , C_{1-6} alquilo, OC_{1-6} alquilo, COOH, $(CH_2)_{0-3}COOH$, $O(CH_2)_{0-3}COOH$, $C(O)OC_{1-6}alquilo$, $C_{1-6}alquilC(O)OC_{1-6}alquilo$, CO-fenilo, $CONH_2$, $CONH$ -fenilo, SO_2NH_2 , $SO_2C_{1-6}alquilo$, OH, o

Fig 2a1

fenilo sustituido opcionalmente por uno o más grupos R^5 , o R^{6b} -X-; R^5 se selecciona de hidrógeno, C_{1-6} alquilo o $C(O)OC_{1-6}$ alquilo, R^{6b} se selecciona de hidrógeno, C_{1-6} alquilo, CH_3 -F, fenilo, naftilo, heterociclilo o C_{3-7} cicloalquilo; y R^{6b} se sustituye opcionalmente por halo, C_{1-6} alquilo, CH_3 -F, CN, NH_2 , COOH y $COOC_{1-6}$ alquilo,

cada a es independientemente 1, 2 ó 3;

R^3 se selecciona de fenilo o un heterociclilo, y R^3 se sustituye opcionalmente por uno o más , grupos R^7 ;

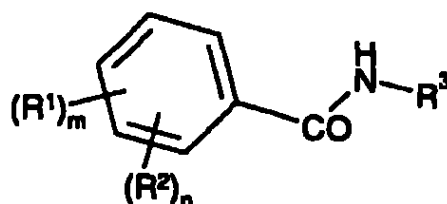
cada R^7 se selecciona independientemente de:

C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, heterociclilo, $(CH_2)_{0-3}C_{3-7}$ cicloalquilo, OH, C_{1-6} alquil-OH, halo, C_{1-6} alquil-halo, OC_{1-6} alquilo, SC_{1-6} alquilo, SH, SO_3 , NH_2 , CN, $NHCHO$, NSO_2C_{1-6} alquilo, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}C(O)OC_{1-6}$ alquilo, $(CH_2)_{0-3}CONH_2$, $(CH_2)_{0-3}CON(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$,

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, C_{3-7} cicloalquilo, OH, C_{1-6} alquil-OH, COOH, $C(O)OC_{1-6}$ alquilo, $N(C_{0-6}alquil)C_{1-6}$ alquilo, $O(C_{0-6}alquil)C_{1-6}$ alquilo, $C_{0-6}alquilOC(O)C_{1-6}$ alquilo, $C(OH)(C_{1-6}alquil)C_{1-6}$ alquilo,

con la condición que cuando R^3 es piridina, entonces R^7 es distinto a COOH o $COOC_{1-6}$ alquilo.

De acuerdo con una característica adicional de la invención se provee un compuesto de Fórmula (Ib) o una sal, solvato o profármaco del mismo.



Fórmula (Ib)

en donde

m es 0, 1 ó 2;

n es 1, 2, ó 3;

y $n + m$ es 2 ó 3;

az
3

cada R^1 se selecciona independientemente de OH, $(CH_2)_{1-4}OH$, CH_3-F_n , $(CH_2)_{1-4}CH_3-F_n$, OCH_3-F_n , halo, OCH_3 , C_2H_5O , $CH_3C(O)O-$, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, NH, C_{1-4} alquilo, -N-di- $(C_{1-4}$ alquil), CN, formilo, fenilo o heterociclilo sustituido opcionalmente por C_{1-6} alquilo;

cada R^2 es el grupo $Y-X-$

con la condición que Y-X no puede ser CH_3O , C_2H_5O ó $CH_3C(O)O-$ en donde cada X es un enlazante seleccionado independientemente de

-O-Z-, -O-Z-O-Z-, -C(O)O-Z-, -OC(O)-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R⁶)-Z-, -N(R⁶)SO₂-Z-, -SO₂N(R⁶)-Z-, -CH=CH-Z-, -C≡C-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z-, -C(O)N(R⁶)S(O)₂-Z-, -S(O)₂N(R⁶)C(O)-Z-, -C(O)-Z-, -Z-, -C(O)-Z-O-Z-, -N(R⁶)C(O)-Z-O-Z-, -O-Z-N(R⁶)-Z-, -O-C(O)-Z-O-Z- o un enlace directo excepto donde Z es C_{1-6} alquilo;

cada Z es independientemente un enlace directo, C_{2-6} alquenileno o un grupo de la fórmula $-(CH_2)_p-C((R^{6a}))_2-(CH_2)_q-$;

cada Y se selecciona independientemente de aril-Z¹-, heterociclil-Z¹-, C_{3-7} cicloalquil-Z¹-, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, - $(CH_2)_{1-4}$ CH_3-F_n o -CH(OH) CH_3-F_n ; en donde cada Y se sustituye independientemente en forma opcional por hasta 3 grupos R⁴;

cada R^4 se selecciona independientemente de halo, - CH_3-F_n , CN, NH₂, C_{1-4} alquilo, -OC C_{1-6} alquilo, -COOH, -C(O)OC C_{1-6} alquilo, OH o fenilo sustituido opcionalmente por C_{1-6} alquilo o -C(O)OC C_{1-6} alquilo,

o R⁵-X¹-, donde X¹ es independientemente como se define en X más arriba y R⁵ se selecciona de hidrógeno, C_{1-6} alquilo, - CH_3-F_n , fenilo, naftilo, heterociclilo o C_{3-7} cicloalquilo; y R⁵ se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: halo, C_{1-6} alquilo, OC C_{1-6} alquilo, - CH_3-F_n , CN, OH, NH₂, COOH, o -C(O)OC C_{1-6} alquilo,

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cada Z^1 es independientemente un enlace directo, C_{2-6} alquenileno o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q$;

R^3 es heterociclilo, en donde el átomo en la posición 2 del anillo heterociclilo relativo al grupo amida, al cual se une R^3 , es un heteroátomo y cuando el átomo en la posición 2 del anillo heterociclilo relativo al grupo amida es nitrógeno, éste es un nitrógeno hibridado SP^2 , y R^3 se sustituye opcionalmente por hasta 2 grupos R^7 ;

R^6 se selecciona independientemente de hidrógeno, C_{1-6} alquilo o $-C_{2-4}$ alquil-O- C_{1-4} alquilo;

R^{6a} se selecciona independientemente de hidrógeno, halo, C_{1-6} alquilo o $-C_{2-4}$ alquil-O- C_{1-4} alquilo;

cada R^7 se selecciona independientemente de:

C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, $(CH_2)_{0-3}$ arilo, $(CH_2)_{0-3}$ heterociclilo, $(CH_2)_{0-3}C_{3-7}$ cicloalquilo, OH, C_{1-6} alquilo, OH, halo, C_{1-6} alquil-halo, OC_{1-6} alquilo, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3 , tioxo, NH_2 , CN, $(CH_2)_{0-3}NH SO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}-O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$; $(CH_2)_{0-3}C(O)NH SO_2-R^8$ y $(CH_2)_{0-3}SO_2NHC(O)-R^8$ en donde una cadena alquilo, anillo cicloalquilo o anillo heterociclilo dentro de R^7 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, -OH, halo, CN, NH_2 , $N-C_{1-4}$ alquilamino, N,N -di- C_{1-4} alquilamino y OC_{1-4} alquilo;

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, arilo, heterociclilo, C_{3-7} cicloalquilo, OH, C_{1-6} alquil-OH, COOH, $C(O)OC_{1-6}$ alquilo, $N(R^6)C_{1-6}$ alquilo, OC_{1-6} alquilo, C_{0-6} alquilOC(O) C_{1-6} alquilo, $C(OH)(C_{1-6}alquil)C_{1-6}alquilo$; en donde una cadena alquilo o arilo, heterociclilo o anillo cicloalquilo dentro de R^8 se sustituye opcionalmente por uno o más sustituyentes seleccionados

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independientemente de: C₁₋₄alquilo, OH, halo, CN, NH₂, -NH-C₁₋₄alquilo, -N-di-(C₁₋₄alquil) y OC₁₋₄alquilo,

cada a es independientemente 1, 2 ó 3;

p es un entero entre 0 y 3;

q es un entero entre 0 y 3;

y $p + q < 4$;

con la condición que

- (i) cuando R³ es 2-piridilo y X es distinto a -Z-, -C(O)-Z-O-Z-, -N(R⁶)-C(O)-Z-O-Z o O-Z-N(R⁶)-Z, entonces R³ no puede ser mono-sustituido en la posición 5 con un grupo R⁷ seleccionado de COOH o C(O)OC₁₋₆alquilo;
- (ii) las posiciones 3, 5 en el anillo fenilo (al cual se unen R¹ y R²) relativo al enlace amida son sustituidas y por lo menos uno de los grupos en la posición 3 y 5 es un grupo R²;
- (iii) una cadena C₁₋₆alquilo no sustituido, no ramificada no puede exceder en longitud a un C₆alquilo;
- (iv) cuando n es 2 ó 3, entonces únicamente un grupo X puede ser -NHC(O)-;
- (v) cuando R³ es piridilo y R⁷ es halo o metilo, entonces el anillo fenilo al cual se une R² no puede ser sustituido por un grupo R² en la posición 2- relativa al enlace amida en donde X es -C(O)NH- y Y es fenilo opcionalmente sustituido, tienilo opcionalmente sustituido o piridilo opcionalmente sustituido;
- (vi) cuando n+m es 2, m es 0 ó m es 1 y R¹ es OH, n es 1 y X es -NHC(O)- ó n es 2 y X se selecciona independientemente de -C(O)NH-, -NHC(O)-, -O-, -S(O₂)NH- o un enlace directo en donde un grupo X es -NHC(O), Y se selecciona de fenilo, ciclohexilo, 4,5-dihidro-5-oxo-pirazolilo, tienilo, 1,3-dihidro-1,3-dioxo-isoindolinilo, 2-oxo 1-benzopirano o piridilo y Y se sustituye opcionalmente por R⁴, entonces R³ no puede ser tiazol no sustituido, 4,5-dihidro-5-oxo-pirazolilo sustituido por triclorofenilo, 4,5,6,7-tetrahidro-benzo[b]tiofeno sustituido por etoxicarbonilo o piridilo

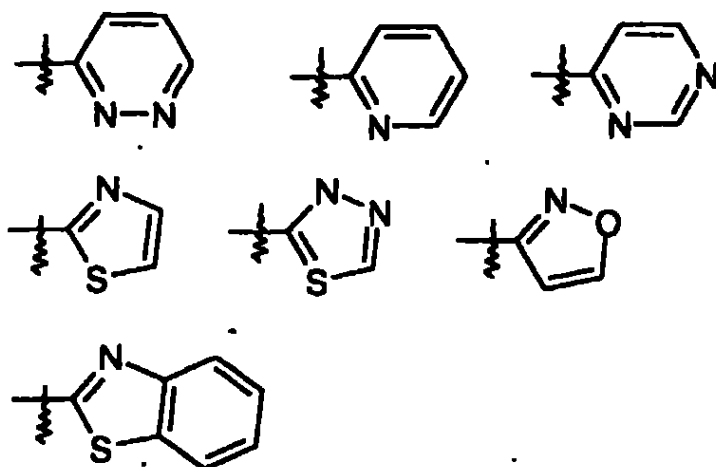
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opcionalmente de manera independiente mono o di-sustituido por metilo, etoxi o propilcarbonilamino; y

- (vii) cuando $n+m$ es 3, m es 0 o 2, R^1 se selecciona independientemente de metilo, metoxi o hidroxilo, n es 1, 2 ó 3, X se selecciona independientemente de $-O-$, $-S(O_2)NH-$, $-C(O)-$, $-S(O_2)-$, $-CH_2-$ o un enlace directo, Y se selecciona de pirrolidinilo, morfolino, fenilo, tetrazolilo o propilo en donde Y se sustituye opcionalmente por R^4 y R^4 se selecciona de di-hidroxilo, metoxi, C_{1-4} alquilo entonces R^3 no puede ser tetrazolilo, tiazolilo no sustituido o tiazolilo sustituido por etoxicarbonilmetilo.

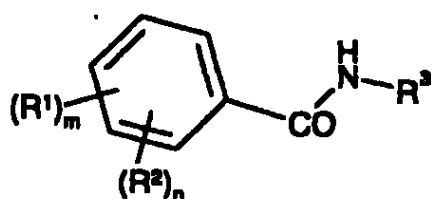
Para evitar dudas, C_6 alquilo es $-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$.

Para evitar dudas, los ejemplos de R^3 en donde R^3 es heterociclilo y el átomo en la posición 2 del anillo heterociclilo R^3 , relativo al grupo amida al cual se une R^3 , es un nitrógeno hibridado sp^2 , comprenden:



en donde  representa el punto de unión al grupo amida.

De acuerdo con una característica adicional de la invención se provee un compuesto de Fórmula (Ic) o una sal del mismo;



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Fórmula (Ic)

en donde

m es 0, 1 ó 2;

n es 0, 1, 2, 3 ó 4;

y $n + m > 0$;

cada R^1 se selecciona independientemente de OH, $(CH_2)_{1-4}OH$, CH_3-aF_a , $(CH_2)_{1-4}CH_3-aF_a$, OCH_3-aF_a , halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, NH_2 , $N(C_{1-6}alquil)C_{2-6}alquilo$, CN, fenilo o un heterociclilo sustituido opcionalmente por C_{1-6} alquilo;

cada R^2 es el grupo Y-X-

en donde cada X es un enlazante seleccionado independientemente de

$-O(CH_2)_{0-3}-$, $-(CH_2)_{0-3}O-$, $-C(O)O(CH_2)_{0-3}-$, $-S(CH_2)_{0-3}-$, $-SO(CH_2)_{0-3}-$, $O_2(CH_2)_{0-3}-$, $-NHSO_2$, $-SO_2NH-$, $-N(CH_2)_{0-3}-$, $-N(CH_2)_{1-3}O(CH_2)_{0-3}-$, $-(CH_2)_{1-4}-$, $-CH=CH(CH_2)_{0-2}-$, $-C\equiv C(CH_2)_{0-2}-$, $-NHCO-$, $-CONH-$;

cada Y se selecciona independientemente de fenil $(CH_2)_{0-2}$, naftil $(CH_2)_{0-2}$, heterociclil $(CH_2)_{0-2}$, C_{3-7} cicloalquil $(CH_2)_{0-2}$, C_{2-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, o $CH(OH)CH_3-aF_a$;

cada Y es independientemente sustituido opcionalmente por uno o más grupos R^4 ;

cada R^4 se selecciona independientemente de halo, CH_3-aF_a , OCH_3-aF_a , CN, NH_2 , C_{1-6} alquilo, $OC_{1-6}alquilo$, COOH, $(CH_2)_{0-3}COOH$, $O(CH_2)_{0-3}COOH$, $C(O)OC_{1-6}alquilo$, $C_{1-6}alquilC(O)OC_{1-6}alquilo$, CO-fenilo, CONH₂, CONH-fenilo, SO₂NH₂, SO₂ C_{1-6} alquilo, OH, o fenilo sustituido opcionalmente por uno o más grupos R^5 , o $R^{6b}-X-$;

R^5 se selecciona de hidrógeno, $C_{1-6}alquil$ o $C(O)OC_{1-6}alquilo$,

R^{6b} se selecciona de hidrógeno, $C_{1-6}alquilo$, CH_3-aF_a , fenilo, naftilo, heterociclilo o C_{3-7} cicloalquilo; y R^{6b} se sustituye opcionalmente por halo, $C_{1-6}alquilo$, CH_3-aF_a , CN, NH_2 , COOH y COOC₁₋₆alquilo,

cada a es independientemente 1, 2 ó 3;

R^3 es un heterociclilo, y R^3 se sustituye opcionalmente por uno o más grupos R^7 ;

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cada R^7 se selecciona independientemente de:

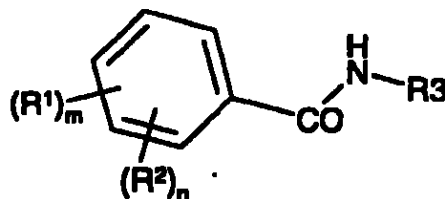
C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, heterociclilo, $(CH_2)_{0-3}C_{3-7}$ cicloalquilo, OH, C_{1-6} alquil-OH, halo, C_{1-6} alquil-halo, OC_{1-6} alquilo, SC_{1-6} alquilo, SH, SO_3 , NH_2 , CN, $NHCHO$, NSO_2C_{1-6} alquilo, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}C(O)OC_{1-6}$ alquilo, $(CH_2)_{0-3}CONH_2$, $(CH_2)_{0-3}CON(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$,

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, C_{3-7} cicloalquilo, OH, C_{1-6} alquil-OH, $COOH$, $C(O)OC_{1-6}$ alquilo, $N(C_{0-6}alquil)C_{1-6}alquilo$, $O(C_{0-6}alquil)C_{1-6}alquilo$, $C_{0-6}alquilOC(O)C_{1-6}alquilo$, $C(OH)(C_{1-6}alquil)C_{1-6}alquilo$,

con la condición que

- (i) cuando R^3 es tiazol y R^7 es nitro, entonces por lo menos un grupo R^2 es distinto a O-prepeno;
- (ii) cuando R^3 es pirimidina o piridina, entonces R^1 es distinto a OH;
- (iii) cuando R^3 es piridina, entonces R^7 es distinto a $COOH$ ó $COOC_{1-6}alquilo$.

Una característica adicional de la invención es un compuesto de Fórmula (Id) o una sal, solvato o profármaco del mismo;



Fórmula (Id)

en donde

R^3 es fenilo, sustituido opcionalmente por uno o más grupos R^7 ;

m , n , R^1 , R^2 , X , Y , R^4 , R^5 , R^6 , R^7 , R^8 , y a son como se definen anteriormente para un Compuesto de Fórmula (I).

Compuestos de Fórmula (I), (Ia), (Ib), (Ic), o (Id) pueden formar sales que están dentro del ámbito de la invención. Se prefieren sales farmacéuticamente aceptables, aunque otras sales pueden ser útiles, por

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ejemplo, en aislar o purificar compuestos.

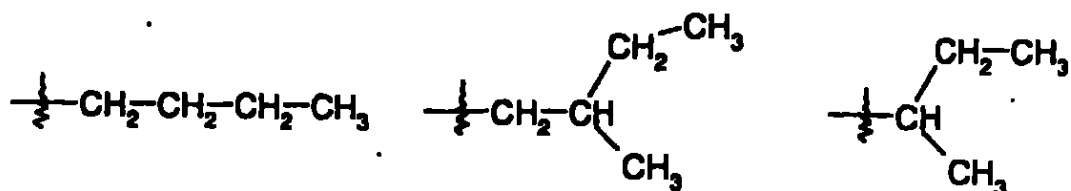
Cuando m es 2, cada grupo R^1 puede ser idéntico o diferente; preferiblemente los dos grupos R^1 son los mismos. Cuando n es 2, 3 ó 4, cada grupo R^2 puede ser idéntico o diferente a cualquier otro grupo R^2 ; preferiblemente por lo menos dos grupos R^2 son diferentes. El grupo(s) R^1 y/o R^2 puede(n) estar unido(s) en las posiciones -2, -3, -4, -5 ó -6.

El término "arilo" se refiere a fenilo, naftilo o a un anillo carbocíclico bicíclico parcialmente saturado que contiene entre 8 y 12 átomos de carbono, preferiblemente entre 8 y 10 átomos de carbono. Ejemplos de anillo carbocíclico bicíclico parcialmente saturado comprenden: 1,2,3,4-tetrahidronaftilo, indanilo, indenilo, 1,2,4a,5,8,8a-hexahidronaftilo o 1,3a-dihidropentaleno.

El término "halo" comprende cloro, bromo, fluoro y yodo; preferiblemente cloro, bromo y fluoro, muy preferiblemente fluoro.

La expresión " $-\text{CH}_3\text{F}_a$ " en donde a es un entero entre 1 y 3 se refiere a un grupo metilo en el cual 1, 2 ó todos los 3 hidrógenos se reemplazan por un átomo de flúor. Los ejemplos comprenden: trifluorometilo, difluorometilo y fluorometilo. Una notación análoga se emplea con referencia al grupo $-(\text{CH}_2)_{1-4}\text{CH}_3\text{F}_a$. Los ejemplos comprenden: 2,2-difluoroetilo y 3,3,3-trifluoropropilo.

En esta especificación el término "alquilo" comprende los dos grupos alquilo de cadena recta o ramificada. Por ejemplo, " C_{1-4} alquilo" comprende propilo, isopropilo y *t*-butilo. Para evitar dudas, una cadena alquilo puede unirse al resto de la molécula en el extremo de una cadena alquilo o en la mitad de una cadena alquilo, es decir, la definición de "alquilo" incluye las siguientes estructuras:



En donde  representa el punto de unión al resto de la molécula.

Un "heterociclilo" es un anillo monocíclico o bicíclico fusionado, saturado, parcialmente saturado o insaturado que contiene 3-12 átomos de los cuales por lo menos un átomo se selecciona de nitrógeno, azufre u oxígeno, en donde un grupo-CH₂- puede reemplazarse opcionalmente por un -C(O)- o átomos de azufre en un anillo heterocíclico pueden oxidarse a S(O) o S(O)₂. A menos que se especifique lo contrario, un anillo heterociclilo puede estar enlazado a carbono o nitrógeno, salvo que el enlazamiento mediante nitrógeno lleve a un nitrógeno cuaternario cargado.

Preferiblemente un "heterociclilo" es un anillo monocíclico o bicíclico fusionado saturado, parcialmente saturado o insaturado, en donde cada anillo contiene 5 ó 6 átomos de los cuales 1 a 3 átomos son nitrógeno, azufre u oxígeno, los cuales pueden, a menos que se especifique lo contrario enlazarse a carbono o nitrógeno, en donde un grupo -CH₂- puede reemplazarse opcionalmente por uno -C(O)- ó átomos de azufre en un anillo heterocíclico pueden oxidarse a grupos S(O) o S(O)₂.

Ejemplos y valores apropiados del término "heterociclilo" son tiazolidinilo, pirrolidinilo, pirrolinilo, 2-pirrolidonilo, 2,5-dioxopirrolidinilo, 2-benzoxazolinonilo, 1,1-dioxotetrahidrotienilo, 2,4-dioxoimidazolidinilo, 2-oxo-1,3,4-(4-triazolinil), 2-oxazolidinonilo, 5,6-dihidrouracililo, 1,3-benzodioxolilo, 1,2,4-oxadiazolilo, 2-azabicyclo[2.2.1]heptilo, 4-tiazolidonilo, morfolino, 2-oxotetrahidrofuranilo, tetrahidrofuranilo, 2,3-dihidrobenzofuranilo, benzotienilo, isoxazolilo, tetrahidropiranilo, piperidilo, 1-oxo-1,3-dihidroisoindolilo, piperazinilo, tiomorfolino, 1,1-dioxotiomorfolino, tetrahidropiranilo, 1,3-dioxolanilo, homopiperazinilo, tienilo, isoxazolilo, imidazolilo, pirrolilo, tiazolilo, tiadiazolilo, isotiazolilo, 1,2,4-triazolilo, 1,2,3-triazolilo, piranilo, indolilo, pirimidilo, tiazolilo, pirazinilo, piridazinilo, piridilo, 4-piridonilo, quinolilo y 1-isoquinolonilo.

Preferiblemente el término "heterociclilo" se refiere anillos heterocíclicos monocíclicos con sistemas de 5 ó 6 miembros, tales como

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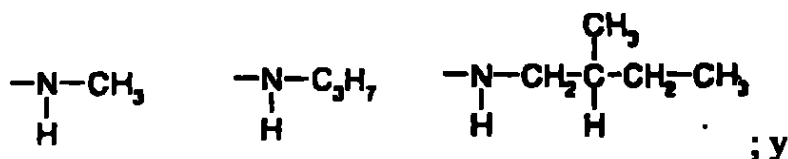
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isoxazolilo, pirrolidinilo, 2-pirrolidonilo, 2,5-dioxopirrolidinilo, morfolino, tetrahidrofuranilo, piperidilo, piperazinilo, tiomorfolino, tetrahidropiranilo, tienilo, imidazolilo, 1,2,4-triazolilo, 1,3,4-triazolilo, indolilo, tiazolilo, tiadiazolilo, pirazinilo, piridazinilo y piridilo.

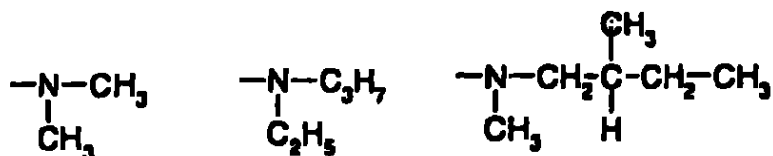
Ejemplos preferidos de sistemas de anillo bicíclico 5/6 y 6/6 comprenden benzofuranilo, benzimidazolilo, benztiofenilo, benzotiazolilo, benzisotiazolilo, benzoxazolilo, benzisoxazolilo, piridoimidazolilo, pirimidoimidazolilo, quinolinilo, isoquinolinilo, quinoxalinilo, quinazolinilo, ftalazinilo, cinnolinilo y naftiridinilo.

El término "cicloalquilo" se refiere a un anillo carbocíclico saturado que contiene entre 3 a 12 átomos de carbono, preferiblemente entre 3 y 7 átomos de carbono. Ejemplos de C₃₋₇-cicloalquilo comprenden cicloheptilo, ciclohexilo, ciclopentilo, ciclobutilo o ciclopropilo. Preferiblemente ciclopropilo, ciclopenilo o ciclohexilo.

Ejemplos de C₁₋₆-alquilo comprenden metilo, etilo, propilo, isopropilo, *sec*-butilo, *tert*-butilo y 2-etil-butilo; ejemplos de C₁₋₆-alquil-OH comprenden hidroximetileno e hidroxietileno; ejemplos de C₁₋₆-alquil-halo comprenden clorometileno, fluorometileno, cloroetileno y fluoroetileno; ejemplos de C₂₋₆-alquenilo comprenden: etenilo, 2-propenilo, 2-butenilo, o 2-metil-2-butenilo; ejemplos de C₂₋₆-alquinilo comprenden: etinilo, 2-propinilo, 2-butinilo, o 2-metil-2-butinilo, ejemplos de -OC₁₋₄-alquilo comprenden metoxi, etoxi, propoxi y *tert*-butoxi; ejemplos de -C(O)OC₁₋₆-alquilo comprenden metoxycarbonilo, etoxycarbonilo y *tert*-butiloxycarbonilo; ejemplos de -NH-C₁₋₄-alquilo comprenden:



ejemplos de -N-di-(C₁₋₄-alquilo):



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Para evitar dudas, en la definición de un grupo enlazante 'X', el lado a mano derecha del grupo se une al anillo fenilo y el lado a mano izquierda se fija a 'Y'. La misma orientación se aplica al grupo enlazante 'X¹'; por consiguiente, el lado a mano derecho de 'X¹' se une a Y y el lado a mano izquierda se fija a 'R⁵'.

Se entiende que, en la medida que algunos de los compuestos de Fórmula (I), (Ia), (Ib), (Ic) y (Id) definidos anteriormente o compuestos de Fórmula (II) a (IIk) definidos más adelante pueden existir en formas racémicas u óptimamente activas en virtud de uno o más átomos de carbono asimétricos, la invención comprende en su definición cualquier forma racémica u óptimamente activa que posea la propiedad de estimular GLK directamente o inhibiendo la interacción GLK/GLKRP. La síntesis de formas ópticamente activas se lleva a cabo por técnicas estándar de química orgánica bien conocidas en el arte, por ejemplo mediante la síntesis de insumos ópticamente activos o mediante resolución de una forma racémica. Tiene que entenderse asimismo que ciertos compuestos pueden existir en formas tautoméricas y que la invención se relaciona con cualquiera y todas las formas tautoméricas de los compuestos de la invención que activan la GLK.

Compuestos preferidos de Fórmula (I), (Ia), (Ib), (Ic), y (Id) más arriba, y de compuestos de Fórmula (II) a (IIk) más adelante son aquellos en los que se aplican uno cualquiera o más de los siguientes:

- (1) m es 0 ó 1;
 n es 1 ó 2; preferiblemente n es 2;
muy preferiblemente m es 0 y n es 2.
- (2) El grupo(s) R¹ y/o R² se une(n) en la posición 2- y/o la posición 3- y/o la posición 5-; cuando $n + m$ es 3, los grupos están preferiblemente en las posiciones 2-, 3- y 5-; cuando $n + m$ es 2, los grupos están preferiblemente en las posiciones 2- y 5- ó las posiciones 3- y 5-; muy preferiblemente hay dos grupos en total, sustituidos en las posiciones 3- y 5-.

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- (3) Cada R^1 se selecciona independientemente de OH, formilo, CH_3-aF_a (preferiblemente CF_3), OCH_3-aF_a , halo, C_{1-6} alquilo, NH_2 , CN, $(OH_2)_{1-4}OH$ o un heterociclilo opcionalmente sustituido por C_{1-6} alquilo;

Preferiblemente R^1 se selecciona de:

OH, formilo, CH_3-aF_a (preferiblemente CF_3), OCH_3-aF_a (preferiblemente OCF_3), halo, C_{1-4} alquilo (preferiblemente metilo), NH_2 , CN y $(CH_2)_{1-4}OH$;

muy preferiblemente R^1 se selecciona de:

OH, formilo, NH_2 , halo (preferiblemente cloro) o $(CH_2)_{1-4}OH$.

- (4) Cada R^2 es el grupo Y-X-

en donde cada X se selecciona independientemente de:

-Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -OC(O)-Z-, -C(O)-Z-O-Z-, -O-C(O)-Z-O-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R⁶)-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z-, -N(R⁶)-C(O)-Z-O-Z-, -SO₂N(R⁶)-Z-, -N(R⁶)SO₂-Z- ó -O-Z-N(R⁶)-Z-;

preferiblemente cada X se selecciona de:

-Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -C(O)-Z-O-Z-, -O-C(O)-Z-O-Z-, -N(R⁶)-Z-, -N(R⁶)CO-Z-, -N(R⁶)-C(O)-Z-O-Z- o -O-Z-N(R⁶)-Z-;

preferiblemente además cada X se selecciona de:

-Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -C(O)-Z-O-Z-, -N(R⁶)-Z-, ó -N(R⁶)CO-Z-;

muy preferiblemente cada X se selecciona de:

-CH=CH-Z-, -O-Z- ó -C(O)-Z-.

cada Z se selecciona independientemente de:

un enlace directo, $-(CH_2)_{1-2}$, o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$, en donde R^{6a} se selecciona independientemente de hidrógeno y C_{1-4} alquilo;

preferiblemente un enlace directo, $-(CH_2)_{1-2}$ o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$,

en donde R^{6a} se selecciona independientemente de hidrógeno y

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C_{1-4} alquilo y p y q son

independientemente 0 ó 1;

más preferiblemente un enlace directo, $-CH_2-$ ó $-C(CH_3)_2-$.

y cada Y se selecciona independientemente de:

C_{1-6} alquilo, C_{2-6} alqueno, aril- Z^1 -, heterociclilo- Z^1 -, C_{3-7} cicloalquil $(CH_2)_{0-2}$, $-(CH_2)_{1-4}CH_3$, F_1

preferiblemente cada Y se selecciona de:

C_{1-6} alquilo (preferiblemente un C_{2-6} alquilo de cadena ramificada tal como isopropilo, isobutilo, etc), C_{2-6} alqueno, fenil- Z^1 - o heterociclilo- Z^1 -;

muy preferiblemente cada Y se selecciona de:

$-CH_3$, $-C_2H_5$, prop-2-ilo, iso-propilo, 1-metil-propilo, 2-metil-propilo, alilo, fenilo, 2-etil-butilo, fenil- Z^1 -, ciclopropil- Z^1 -, ciclopentil- Z^1 -, morfolino- Z^1 -, piperidinil- Z^1 -, piperazinil- Z^1 -, pirrolidinil- Z^1 -, tetrahidro-2H-pirani- Z^1 -, isoxazolil- Z^1 -, oxazolil- Z^1 -, piridil- Z^1 -, tiazolil- Z^1 -, tienil- Z^1 - o isoindolinil- Z^1 -,

cada Z^1 se selecciona independientemente de:

un enlace directo, $-(CH_2)_{1-2}$, o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$, en donde R^{6a} se selecciona independientemente de hidrógeno y C_{1-4} alquilo;

preferiblemente un enlace directo, $-(CH_2)_{1-2}$ o un grupo de la

fórmula

$-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$, en donde R^{6a} se selecciona independientemente de hidrógeno y C_{1-2} alquilo y p y q son independientemente 0 ó 1;

preferiblemente además un enlace directo, $-CH_2-$, $-CH_2-CH(CH_3)-$ ó $-(CH_2)_2-$; muy preferiblemente un enlace directo, $-CH_2-$ ó $-(CH_2)_2-$

en donde en cada uno del anterior Y se sustituye independientemente en forma opcional por R^4 .

(5) Cada R^2 es el grupo Y-X-, Z en la definición de X es un enlace

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directo y Z^1 en la definición de Y es un grupo de la fórmula -
 $(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$.

- (6) Cada R^4 se selecciona independientemente de
 halo, CH_3-xF_x (idealmente CF_3), OCH_3-xF_x (idealmente OCF_3),
 CN, C_{1-6} alquilo, OC_{1-6} alquilo, COOH, $C(O)OC_{1-6}$ alquilo,
 $(CH_2)_{0-3}COOH$, $O(CH_2)_{0-3}COOH$, CO-fenilo, $CONH_2$,
 $CONH$ -fenilo, SO_2NH_2 , SO_2C_{1-6} alquilo, OH, o fenilo
 opcionalmente sustituido por uno o más grupos R^5 donde R^5
 se selecciona de hidrógeno, C_{1-6} alquilo o $C(O)OC_{1-6}$ alquilo;
 preferiblemente cada R^4 se selecciona de
 halo, CN, C_{1-6} alquilo, OC_{1-6} alquilo o COOH.
- (7) cada R^5 se selecciona de:
 C_{1-6} alquilo, fenilo, heterociclilo o C_{3-7} cicloalquilo;
 preferiblemente cada R^5 se selecciona de:
 C_{1-6} alquilo, tetrahydrofuranilo, imidazolilo, isoxazolilo,
 pirazinilo, pirimidinilo, tienilo, 1,3-benzodioxol, ciclopropilo,
 ciclobutilo, ciclopentilo o ciclohexilo;
 muy preferiblemente cada R^5 se selecciona de:
 CH_3 , C_2H_5 , prop-2-ilo, tetrahydrofuranilo, imidazolilo,
 isoxazolilo, pirazinilo, pirimidinilo, tienilo, 1,3-benzodioxolilo
 o ciclopentilo;
- (8) cada X^1 se selecciona independientemente de:
 un enlace directo, -Z-, -O-C(O)-Z-, -C(O)-O-Z-, -C(O)-Z-, -
 $N(R^6)-C(O)-Z-$, -C(O)-N(R^6)-Z-, -S(O₂)-Z-, -N(R^6)SO₂-Z- ó -
 $SO_2N(R^6)-Z-$;
 preferiblemente cada X^1 se selecciona independientemente de:
 un enlace directo, -Z-, -O-C(O)-Z-, -C(O)-Z-, $N(R^6)-C(O)-Z-$
 ó -S(O₂)-Z-;
 muy preferiblemente cada X^1 se selecciona independientemente
 de:
 un enlace directo, -CH₂-, -O-C(O)-, -C(O)-, -N(CH₃)-C(O)-
 CH₂- ó -S(O)₂-;

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- (9) sustituyentes opcionales en R^5 se seleccionan independientemente de:

OH, CN, NH_2 , C_{1-6} alquilo, OC_{1-6} alquilo o halo;

preferiblemente sustituyentes opcionales en R^5 se seleccionan independientemente de:

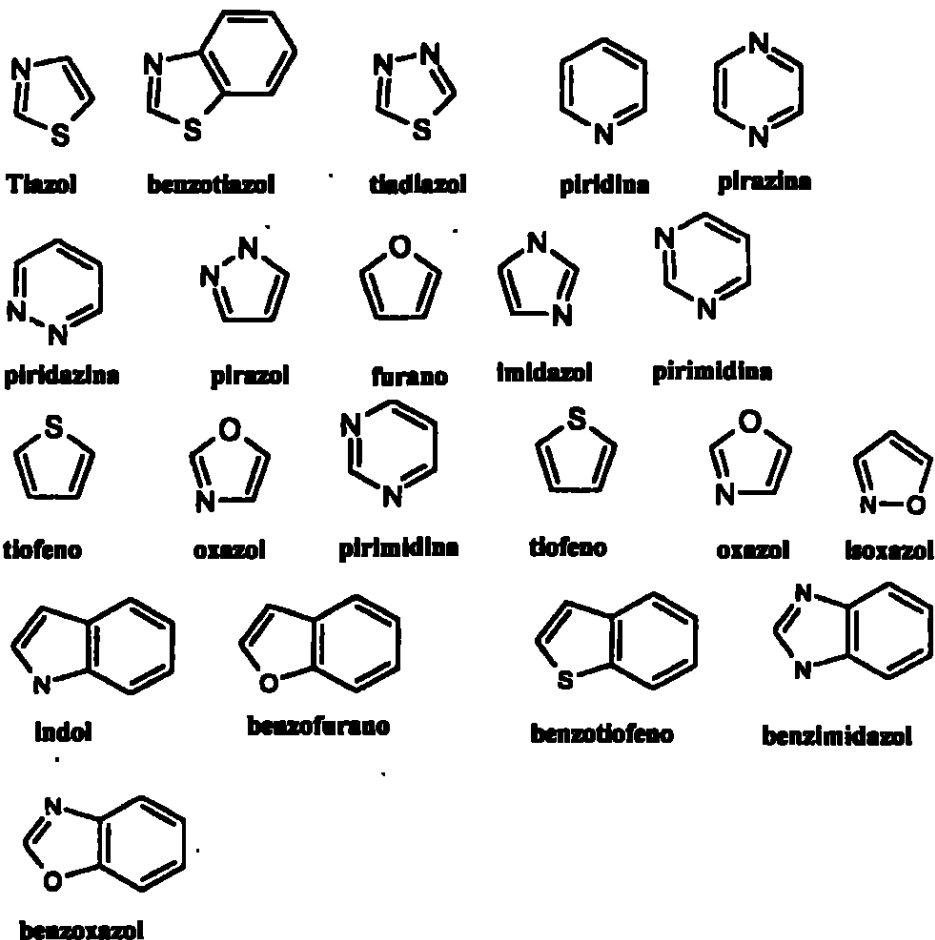
OH, C_{1-6} alquilo, OC_{1-6} alquil o halo;

muy preferiblemente sustituyentes opcionales en R^5 se seleccionan independientemente:

OH, CH_3 , t-butilo, OCH_3 , cloro o fluoro;

- (10) R^3 es un heterociclilo (preferiblemente un grupo heterociclilo con contenido de nitrógeno), opcionalmente sustituido por uno o más grupos R^7 ;

preferiblemente R^3 es un heterociclilo seleccionado de los siguientes:



Más preferiblemente R^3 se selecciona de:

thiazol, tiadiazol, piridina, pirazina, piridazina, pirazol, pirimidina, isoxazol, furano, benzotiazol, benzimidazol y

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benzoxazol.

Preferiblemente además R^3 se selecciona de:

tiazol, benzotiazol, tiadiazol, piridina, pirazina, piridazina, pirazol, imidazol, pirimidina, oxazol e indol.

Muy preferiblemente R^3 se selecciona de:

piridina, tiazol o tiadiazol.

En una incorporación adicional de la invención, R^3 se selecciona de:

benzotiazol, tiazol, tiadiazol, piridina, pirazina, piridazina, pirazol, pirimidina, isoxazol y furano.

(11) R^3 no se sustituye o se sustituye por un grupo R^7 .

(12) Cada R^7 se selecciona independientemente de:

OH, CN, NH_2 , SO_3 , tioxo, halo, C_{1-6} alquilo, C_{1-6} alquil-OH, O- C_{1-6} alquilo, C_{1-6} alquil-halo, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $-(CH_2)_{0-3}S(O)_{0-2}R^8$, $-(CH_2)_{0-3}N(R^6)SO_2R^8$, $(CH_2)_{0-3}C(O)N(R^6)S(O)_2R^8$ ó $(CH_2)_{0-3}$ heterociclilo;

preferiblemente R^7 se selecciona de:

OH, CN, NH_2 , SO_3 , tioxo, halo, C_{1-4} alquilo, C_{1-4} alquil-OH, O- C_{1-4} alquilo, C_{1-4} alquil-halo, $(CH_2)_{0-1}COOH$, $(CH_2)_{0-1}C(O)OR^8$, $(CH_2)_{0-1}NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}NHC(O)(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$, $-(CH_2)_{0-2}S(O)_{0-2}R^8$, $-(CH_2)_{0-1}N(R^6)SO_2R^8$, $(CH_2)_{0-1}C(O)N(R^6)S(O)_2R^8$ ó $(CH_2)_{0-1}$ heterociclilo (preferiblemente el heterociclilo se selecciona de furanilo, morfolino, 5-oxo-oxadiazolilo o tetrazolilo);

preferiblemente además R^7 se selecciona de:

$COOH$, $C(O)OC_{1-6}$ alquilo, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-3}C(O)NH(SO_2-R^8)$ o $(CH_2)_{0-3}SO_2NHC(O)-R^8$;

muy preferiblemente R^7 se selecciona de:

$COOH$, $C(O)OC_{1-6}$ alquilo o $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$,

(13) R^8 se selecciona de:

hidrógeno, OH, $COOH$, C_{1-6} alquilo, O- C_{1-6} alquilo, $-C(O)-O-$

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C_{1-6} alquilo, C_{0-6} alquilOC(O) C_{1-6} alquilo, $N(R^6)C_{1-6}$ alquilo, arilo, heterociclilo o C_{3-7} cicloalquilo;

preferiblemente R^8 se selecciona de:

hidrógeno, OH, COOH, CH_3 , isopropilo, 2-metil-butilo, pent-3-ilo, $-O-CH_3$, $-C(O)-O-C_2H_5$, $-CH_2-O-C(O)-CH_3$, $-CH_2-O-C(O)-C_2H_5$, $-C(CH_3)_2-O-C(O)-CH_3$, NH-isopropilo, NH-*t*-butilo, $N(CH_3)-CH_3$, fenilo, isoxazolilo, pirazolilo, piridilo, tienilo, ciclopropilo o ciclobutilo;

(14) sustituyentes opcionales preferidos en R^8 se seleccionan independientemente de:

OH, CN, NH_2 , halo o C_{1-6} alquilo;

sustituyentes opcionales más preferidos en R^8 se seleccionan independientemente de:

OH, halo o C_{1-6} alquilo;

sustituyentes opcionales más preferidos en R^8 se seleccionan independientemente de :

OH, cloro, fluoro y CH_3 .

Por ejemplo, compuestos particularmente preferidos de la invención son aquellos en donde:

m es 0 y n es 2, los dos grupos R^2 se unen en las posiciones 2- y 5- o las posiciones 3- y 5- (idealmente las posiciones 3- y 5-), y X es $-O(CH_2)_{0-2}-$ (idealmente $-OCH_2-$); o

m es 0 y n es 2, los dos grupos R^2 se unen en las posiciones 2- y 5- o las posiciones 3- y 5- (idealmente las posiciones 3- y 5-), X es $-O(CH_2)_{0-2}-$ (idealmente $-O-$ ó $-OCH_2-$), y Y es bencilo opcionalmente sustituido por halo (tal como fluoro o cloro, idealmente fluoro) o C_{1-6} alquilo; o

m es 0 y n es 2, los dos grupos R^2 se unen en las posiciones 2- 5- o las posiciones 3- y 5- (idealmente las posiciones 3- y 5-), X es $-O(CH_2)_{0-2}-$ (idealmente $-O-$ ó $-OCH_2-$), y R^3 es un heterociclilo opcionalmente sustituido por R^7 ; o

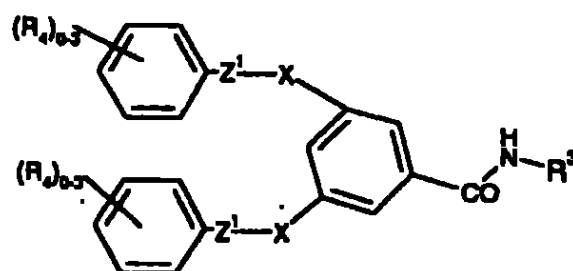
m es 0 y n es 2, los dos grupos R^2 se unen en las posiciones 2- y

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5- o las posiciones 3- y 5- (idealmente las posiciones 3- y 5-), X es -O- ó -O(CH₂)₀₋₂- (idealmente -O- ó -OCH₂-), Y es fenilo opcionalmente sustituido por halo (tal como fluoro o cloro, idealmente fluoro) o C₁-alquilo, y R³ es un heterociclilo opcionalmente sustituido por R⁷; o

m es 1 y n es 1, los grupos R¹ y R² se unen en las posiciones 2- y 5- o las posiciones 3- y 5- (idealmente las posiciones 3- y 5-), R¹ es halo (tal como fluoro, cloro), y X es -O(CH₂)₀₋₂- (idealmente -O- ó -OCH₂-).

De acuerdo con una característica adicional de la invención se proveen los siguientes grupos preferidos de compuestos de la invención: (I) un compuesto de Fórmula (II)

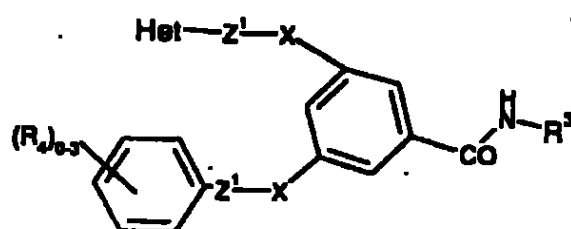


Fórmula (II)

en donde:

X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I); o una sal, solvato o pro-fármaco del mismo.

(II) un compuesto de Fórmula (IIa)



Fórmula (IIa)

en donde:

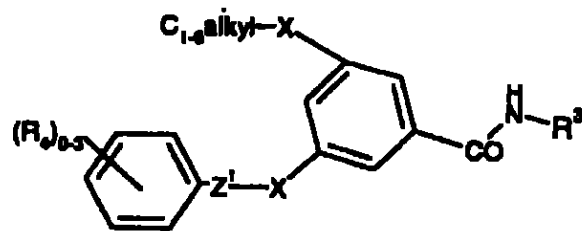
Het es un heterociclilo monocíclico, opcionalmente sustituido con hasta 3 grupos seleccionados de R⁴ y,

X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I);

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o una sal, solvato o pro-fármaco del mismo.

(III) un compuesto de Fórmula (IIb)



Fórmula (IIb)

en donde:

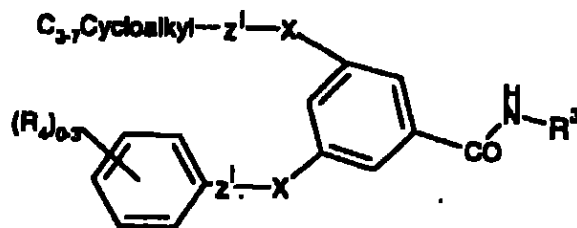
el grupo C₁₋₆alquilo se sustituye opcionalmente con hasta 3 grupos seleccionados de R⁴,

preferiblemente no sustituidos;

el grupo C₁₋₆alquilo contiene opcionalmente un doble enlace, preferiblemente el grupo C₁₋₆alquilo no contiene un doble enlace; y X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I);

o una sal, solvato o pro-fármaco del mismo.

(IV) un compuesto de Fórmula (IIc)



Fórmula (IIc)

en donde:

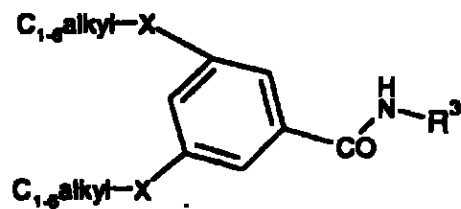
el grupo C₃₋₇cicloalquilo se sustituye opcionalmente con hasta 3 grupos seleccionados de R⁴, y

X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I);

o una sal, solvato o pro-fármaco del mismo.

(V) un compuesto de Fórmula (IId)

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Fórmula (IIId)

en donde:

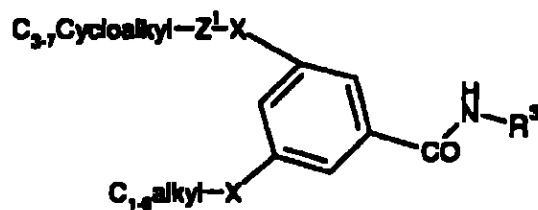
los grupos C₁₋₆alquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de R⁴, preferiblemente uno de los grupos C₁₋₆alquilo es no sustituido,

los grupos C₁₋₆alquilo contienen independientemente en forma opcional un doble enlace, preferiblemente sólo uno de los grupos C₁₋₆alquilo contiene un doble enlace, preferiblemente ninguno de los dos grupos C₁₋₆alquilo contiene un doble enlace, y

X, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I);

o una sal, solvato o pro-fármaco del mismo.

(VI) un compuesto de Fórmula (IIe)



Fórmula (IIe)

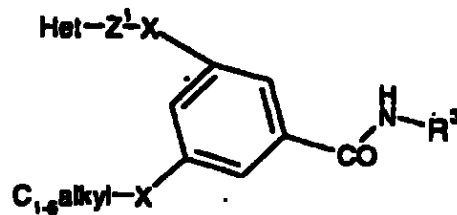
en donde:

los grupos C₃₋₇cicloalquilo y C₁₋₆alquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de R⁴, preferiblemente el grupo C₁₋₆alquilo es no sustituido; el grupo C₁₋₆alquilo contiene opcionalmente un doble enlace, preferiblemente el grupo C₁₋₆alquilo no contiene un doble enlace; y

X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I);

o una sal, solvato o pro-fármaco del mismo.

(VII) un compuesto de Fórmula (IIf)



Fórmula (IIf)

en donde:

Het es un heterociclilo monocíclico,

el Het y los grupos C₁₋₆alquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de R⁴, preferiblemente el grupo C₁₋₆alquilo es no sustituido;

el grupo C₁₋₆alquilo contiene opcionalmente un doble enlace, preferiblemente el grupo C₁₋₆alquilo no contiene un doble enlace; y

X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I); o una sal, solvato o pro-fármaco del mismo.

Un grupo adicional preferido de compuestos de grupo (VII) comprende compuestos de Fórmula (IIf) en donde:

Het es un heterociclilo monocíclico saturado;

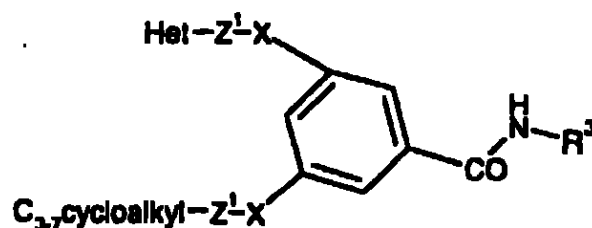
X es -Z-, preferiblemente -CH₂-;

R⁴ es un grupo de R⁵X¹-;

X¹ es como se define para un compuesto de Fórmula (I);

R⁵ es C₁₋₆alquilo, fenilo, heterociclilo, cada uno de los cuales se sustituye opcionalmente como se define para un compuesto de Fórmula (I);

(VIII) un compuesto de Fórmula (IIg)



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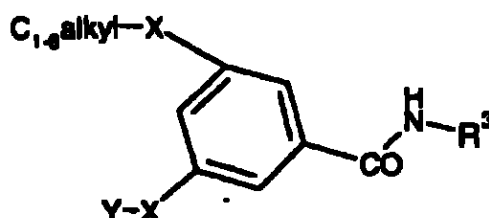
Fórmula (IIg)

en donde:

Het es un heterociclilo monocíclico,

el Het y los grupos C₃₋₇cicloalquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de R⁴, y X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I); o una sal, solvato o pro-fármaco del mismo.

(IX) un compuesto de Fórmula (IIh)



Fórmula (IIh)

en donde:

Y es aril-Z¹-, en donde arilo es preferiblemente un anillo carbocíclico bicíclico parcialmente saturado;

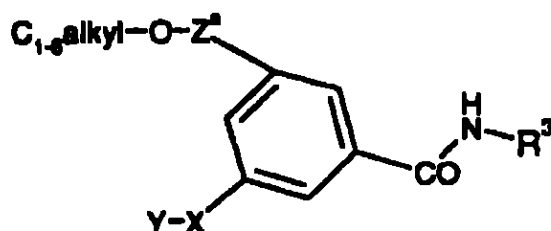
Y y el grupo C₁₋₆alquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de R⁴, preferiblemente el grupo C₁₋₆alquilo es no sustituido,

El grupo C₁₋₆alquilo contiene adicionalmente un doble enlace, preferiblemente el grupo C₁₋₆alquilo no contiene un doble enlace;

y

X, Z¹, R³ y R⁴ son como se definen anteriormente en un compuesto de Fórmula (I); o una sal, solvato o pro-fármaco del mismo.

(X) un compuesto de Fórmula (IIj)



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Fórmula (IIj)

en donde:

X se selecciona de $-\text{SO}_2\text{N}(\text{R}^6)-\text{Z}-$ ó $-\text{N}(\text{R}^6)\text{SO}_2-\text{Z}-$, preferiblemente **X** es $-\text{SO}_2\text{N}(\text{R}^6)-\text{Z}-$;

Z es como se describe anteriormente, preferiblemente **Z** es propileno, etileno o metileno, más preferiblemente **Z** es metileno;

Z' se selecciona de un enlace directo o un grupo de la fórmula $-(\text{CH}_2)_p-\text{C}(\text{R}^{6a})_2-(\text{CH}_2)_q-$;

preferiblemente **Z'** se selecciona de C_{1-2} alquileo o un enlace directo; preferiblemente **Z'** es un enlace directo;

R^{6a} se selecciona de: C_{1-4} alquilo o hidrógeno, preferiblemente metilo o hidrógeno;

Y se selecciona de aril-**Z'**- o heterociclil-**Z'**-;

Y y el grupo C_{1-6} alquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de **R**⁴,

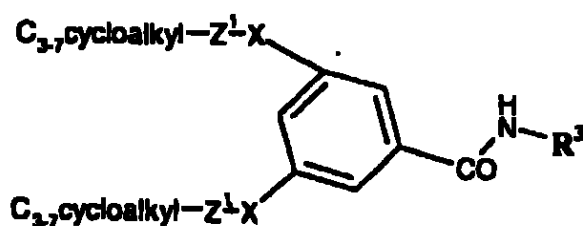
El grupo C_{1-6} alquilo contiene adicionalmente un doble enlace, preferiblemente el grupo C_{1-6} alquilo no contiene un doble enlace, y

Z¹, **R**³ y **R**⁴ son como se definen anteriormente en un compuesto de

Fórmula (I);

o una sal, solvato o pro-fármaco del mismo.

(XI) un compuesto de Fórmula (IIk)



Fórmula (IIk)

en donde:

los grupos C_{3-7} cicloalquilo se sustituyen independientemente en forma opcional con hasta 3 grupos seleccionados de **R**⁴, y

X, **Z**¹, **R**³ y **R**⁴ son como se definen anteriormente en un compuesto de Fórmula (I); o una sal, solvato o pro-fármaco del mismo.

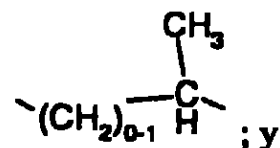
Un grupo adicional preferido de compuestos de la invención en

cualquiera de los grupos (I)-(XI) anteriores es en donde:

X se selecciona independientemente de: $-O-Z-$, $SO_2N(R^6)-Z-$ o $-N(R^6)-Z-$;

Z es un enlace directo o $-CH_2-$;

Z¹ se selecciona de un enlace directo, $-CH_2-$, $-(CH_2)_2$ o



R³ es como se define anteriormente en un compuesto de Fórmula (I); o una sal, solvato o pro-fármaco del mismo.

Un grupo adicional preferido de compuestos de la invención en uno cualquiera de los grupos (I)-(XI) anteriores es en donde:

R³ se sustituye por al menos un grupo **R⁷** (preferiblemente un grupo **R⁷**);

R⁷ es un grupo de la fórmula $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}N(R^6)S(O)_2R^8$ o $(CH_2)_{0-3}$ heterociclilo (preferiblemente 5-oxo-1,2,4-oxadiazol-3-ilo o -tetrazol-5-ilo);

R³, **R⁶** y **R⁸** son como se definen anteriormente en un compuesto de Fórmula (I);

o una sal, solvato o pro-fármaco del mismo.

Los compuestos de la invención pueden administrarse en la forma de un pro-fármaco. Un pro-fármaco es un bioprecursor o compuesto farmacéuticamente aceptable que es susceptible de degradarse en el organismo 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). En el arte se conocen varias formas de profármacos. Para ejemplos de tales derivados de profármaco, véase:

a) Design of Prodrugs (Diseño de Profármacos), editado por H; Bundgaard, (Elsevier, 1985) y Methods in Enzymology (Métodos en Enzimología), Vol. 42, página 309-396, editado por K. Widder, y colegas (Academic Press, 1985);

(b) Un libro de texto de Diseño y Desarrollo de Medicamentos, editado

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por Krogsgaard-Larsen;

(c) H. Bundgaard, Capítulo 5 "Design and Application of Prodrugs" (Diseño y Aplicación de Profármacos), por H. Bundgaard páginas 113-191 (1991);

(d) H. Bundgaard, Advanced Drug Delivery Reviews (Reseñas de Administración Avanzada de Fármacos), 8, 1-38(1992);

(e) H. Bundgaard, y *colegas*, Journal of Pharmaceutical Sciences (Diario de Ciencias Farmacéuticas), 77, 285 (1988); y

(f) N. Kaqueya, y *colegas*, Chem Pharm Bull, 32, 692 (1984).

El contenido de los documentos anteriormente citados se incorpora aquí por referencia.

Ejemplos pro-fármacos 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 comprenden ésteres C₁ ó C₆alcoximetilo, por ejemplo, metoximetilo, ésteres C₁ a ₆alcanoiloximetilo, por ejemplo, pivaloiloximetilo, ésteres ftalidilo, ésteres C₃ a ₈cicloalcoxycarboniloxiC₁ a ₆alquilo, por ejemplo, 1-ciclohexilcarboniloxietilo; ésteres 1,3-dioxolen-2-onilmetilo, por ejemplo, 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres C₁₋₆alcoxycarboniloxietilo.

Un éster hidrolizable in-vivo de un compuesto de la invención que contiene un grupo hidroxi comprende ésteres inorgánicos tales como ésteres de fosfato (incluidos ésteres cíclicos fosforamídicos) y éteres α-aciloxialquilo y compuestos relacionados, que como resultado de la hidrólisis in-vivo de la descomposición del éster producen el grupo/grupos precursor/precursores hidroxi. Ejemplos de éteres α-aciloxialquilo comprenden acetoximetoxi y 2,2-dimetilpropioniloxi-metoxi. Una selección de grupos formadores de ésteres hidrolizables in-vivo para hidroxi comprenden alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxycarbonilo (para producir ésteres de carbonato de alquilo), dialquilcarbamoilo y N-(dialquilaminoetil)-N-alquilcarbamoilo (para

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producir carbamatos), dialquilaminoacetilo y carboxiacetilo.

Una sal farmacéuticamente aceptable de un compuesto de la invención es, por ejemplo, una sal de adición de ácido de un compuesto de la invención que es suficientemente básica, por ejemplo, una sal de adición de ácido con, por ejemplo, un ácido orgánico o inorgánico, por ejemplo ácido clorhídrico, bromídrico, sulfúrico, fosfórico, trifluoroacético, cítrico maleico. Adicionalmente, una sal farmacéuticamente aceptable de un derivado de benzoxazinona de la invención que es suficientemente ácida es una sal de metal alcalino, por ejemplo una sal de sodio o de potasio, una sal de metal alcalinotérreo, por ejemplo una sal de calcio o magnesio, 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.

Una característica adicional de la invención es una composición que comprende un compuesto de Fórmula (I) a (Id) o (II) a (IIk) como se define anteriormente, o una sal, solvato o profármaco del mismo, junto con un transportador o diluyente farmacéuticamente aceptable.

De acuerdo con otro aspecto de la invención se provee un compuesto de Fórmula (Ib) a (Id), o (II) a (IIk) como se define anteriormente para uso como un medicamento;

Con la condición que cuando R^3 es 2-piridilo y X es distinto a -Z-, -C(O)-Z-O-Z-, -N((R^6)-C(O)-Z-O-Z- o -O-Z-N(R^6)-Z-, entonces R^3 no puede ser mono-sustituido en la posición 4- con un grupo R^7 seleccionado de COOH ó C(O)OC₁₋₆alquilo.

Además, de acuerdo con la invención se provee un compuesto de Fórmula (Ib) a (Id), o (II) a (IIk) para uso en la preparación de un medicamento para el tratamiento de una enfermedad mediada por GLK, en particular diabetes tipo 2.

El compuesto se formula convenientemente como una composición farmacéutica para ser usada de esta manera.

De acuerdo con otro aspecto de la presente invención se provee un

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método de tratar enfermedades mediadas por la GLK, especialmente diabetes, administrando una cantidad efectiva de un compuesto de Fórmula (Ib) a (Id), o (II) a (IIk), o sal, solvato o pro-fármaco del mismo, a un mamífero necesitado de dicho tratamiento.

Enfermedades específicas que pueden tratarse por el compuesto o composición de la invención comprenden: descenso en la glucosa sanguínea en diabetes mellitus tipo 2 sin un serio riesgo de hipoglicemia (y potencial para tratar tipo 1), dislipidemia, obesidad, resistencia a la insulina, síndrome X metabólico, tolerancia disminuida a la glucosa.

Como se discutió más arriba, entonces el sistema GLK/GLKRP puede describirse como una potencial diana de la "diabesidad" (benéfica tanto en diabetes como en obesidad). Así, de acuerdo con otro aspecto de la invención se provee el uso de un compuesto de Fórmula (Ib) a (Id), o (II) a (IIk), o sal, solvato o pro-fármaco del mismo, en la preparación de un medicamento para uso en el tratamiento combinado o prevención de diabetes y obesidad.

De acuerdo con otro aspecto de la invención se provee el uso de un compuesto de Fórmula (Ib) a (Id), o (II) a (IIk), o sal, solvato o pro-fármaco del mismo, en la preparación de un medicamento para uso en el tratamiento o prevención de la 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 (Ib) a (Id), o (II) a (IIk), o sal, solvato o pro-fármaco del mismo, 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 (Ib) a (Id), o (II) a (IIk), o sal, solvato o pro-fármaco del mismo, a un mamífero necesitado de dicho tratamiento.

Las composiciones de la invención pueden estar en una forma apropiada para uso oral (por ejemplo como tabletas, pastillas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos

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dispersables o gránulos, jarabes o elixires), 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 administración intravenosa, subcutánea, intramuscular o como un supositorio para administración rectal).

Las composiciones de la invención pueden obtenerse por procedimientos convencionales usando excipientes farmacéuticos convencionales, bien conocidos en el arte. Por consiguiente, las composiciones previstas para 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 comprenden, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y desintegrantes tales como almidón de maíz o ácido algérico; agentes aglutinantes tales como almidón; agentes lubricantes tales como estearato de magnesio, ácido estearico o talco; agentes preservantes tales como p-hidroxibenzoato de etilo o propilo, y anti-oxidantes, tales como ácido ascórbico. Formulaciones de tableta pueden ser recubiertas o no cubiertas para modificar su desintegración y la absorción subsiguiente del ingrediente activo en el tracto gastrointestinal, o para mejorar su estabilidad y/o apariencia, en cualquiera de los casos, utilizando agentes recubridores convencionales y procedimientos bien conocidos en el arte.

Composiciones para uso oral puede 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 generalmente el ingrediente



activo en forma finamente pulverizada junto con uno o más agentes de suspensión, tales como carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinil-pirrolidona, goma tragacanto y goma de acacia; agentes dispersantes o humectantes tales como lecitina o productos de condensación de un óxido de alquileo con ácidos grasos (por ejemplo estearato de polyoxetileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como polioxietilen sorbitol monooleato, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o producto de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como polioxietilen sorbitol monooleato, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo polietilen sorbitán monooleato. Las suspensiones acuosas pueden contener además uno o más preservantes (tales como p-hidroxibenzoato de etilo o propilo, anti-oxidantes (tales como ácido ascórbico), agentes colorantes, agentes saborizantes, y/o agentes edulcorantes (tales como sucrosa, sacarina o aspartame).

Suspensiones oleosas pueden formularse suspendiendo el ingrediente activo en un aceite vegetal (tal como aceite de cacahuete, aceite de oliva, aceite de ajonjolí o aceite de coco) o en un aceite mineral (tal como parafina líquida). Las suspensiones oleosas pueden contener un agente espesante tal como cera de abejas, parafina dura o alcohol cetílico. Pueden agregarse agentes edulcorantes tales como los expuestos anteriormente, y agentes saborizantes para proveer una preparación oral agradable. Estas composiciones pueden preservarse por la adición de un anti-oxidante tal como ácido ascórbico.

Polvos dispersables y gránulos apropiados para preparación de una suspensión acuosa por adición de agua contienen generalmente el ingrediente activo junto con un agente dispersante o humectante, agente de

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suspensión y uno o más preservantes. Agentes dispersantes o humectantes apropiados y agentes de suspensión se ejemplifican por aquellos que ya se mencionaron más arriba. De igual manera pueden estar presentes excipientes adicionales tales como agentes edulcorantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención pueden estar asimismo en la forma de emulsiones aceite-en-agua. La fase oleosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de cacahuete, o un aceite mineral, tal como por ejemplo parafina líquida o una mezcla de cualquiera de éstos. Agentes emulsificantes apropiados pueden ser, por ejemplo, gomas de ocurrencia natural tales como goma de 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 sorbitán monooleato) y productos de condensación de dichos ésteres parciales con óxido de etileno tales como polioxietilen sorbitán monooleato. Las emulsiones pueden contener además agentes edulcorantes, saborizantes y preservantes.

Pueden formularse jarabes y elíxires con agentes edulcorantes tales como glicerol, propilen glicol, sorbitol, aspartame o sucrosa, y pueden contener también un agente emoliente, preservante, saborizante y/o colorante.

Las composiciones farmacéuticas pueden estar igualmente en la forma de una suspensión estéril inyectable acuosa u oleosa, que puede formularse de acuerdo con procedimientos conocidos que utilizan uno o más de los agentes dispersantes o humectantes apropiados y agentes de suspensión, que ya se han mencionado más arriba. Una preparación estéril inyectable puede ser asimismo una solución estéril inyectable o suspensión en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo una solución en 1,3-butanediol.

Las composiciones para administración por inhalación pueden estar en la forma de un aerosol convencional presurizado dispuesto para dispensar el ingrediente activo como un aerosol que contiene sólido

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finamente dividido o gotículas de líquido. Pueden utilizarse propulsores convencionales de aerosol tales como hidrocarburos fluorinados volátiles o hidrocarburos, y el dispositivo aerosol se dispone convenientemente para dispensar una cantidad medida de ingrediente activo.

Para mayor información acerca de la formulación se remite al lector al capítulo 25.2 en volumen 5 del Comprehensive Medicinal Chemistry (Corwin Hansch; director de la junta editorial), Pergamon Press 1990.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una forma farmacéutica única variará necesariamente dependiendo del anfitrión tratado y la vía particular de administración. Por ejemplo, una formulación prevista para administración oral a humanos contendrá generalmente, por ejemplo, de 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 generalmente alrededor de 1 mg a alrededor de 500 mg de un ingrediente activo. Para mayor información sobre las Vías de Administración y Regímenes de Dosificación se remite al lector al capítulo 25.3 en volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; director de la junta editorial), 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) variarán naturalmente de acuerdo con la índole y gravedad de las condiciones, la edad y el sexo del animal o paciente y la vía de administración de acuerdo con principios bien conocidos de medicina.

Al utilizar un compuesto de la Fórmula (I), (Ia), (Ib), (Ic) o (Id) para efectos terapéuticos o profilácticos se administrará generalmente de tal 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 dividida. En general, se administrarán dosis más bajas cuando se emplea una vía parenteral. Así, por ejemplo, para administración intravenosa, se utilizará generalmente una dosis en el rango de, por ejemplo, 0.5 mg a 30

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mg por kg de peso corporal. Análogamente, para administración por inhalación, se empleará una dosis en el rango de, por ejemplo, 0.5 mg a 25 mg por kg de peso corporal. Sin embargo, se prefiere la administración oral.

La elevación de la actividad GLK descrita aquí puede aplicarse como terapia única o puede comprender, además del objeto de la presente invención, una o más de otras sustancias y/o tratamientos. 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 comprender las siguientes categorías principales de tratamiento:

- 1) Insulina y análogos de insulina;
- 2) Secretagogos de insulina que comprenden sulfonilureas (por ejemplo glibenclamida, glipizida) y reguladores de glucosa prandial (por ejemplo repaglinida, nateglinida);
- 3) Agentes sensibilizantes a la insulina incluidos agonistas PPAR γ (por ejemplo pioglitazona y rosiglitazona);
- 4) Agentes que suprimen la producción de glucosa hepática (por ejemplo metformina).
- 5) Agentes diseñados para reducir la absorción de glucosa del intestino (por ejemplo acarbosa);
- 6) Agentes diseñados para tratar las complicaciones de hiperglicemia prolongada;
- 7) Agentes anti-obesidad (por ejemplo sibutramina y orlistat);
- 8) Agentes anti-dislipidemia tales como, inhibidores de HMG-CoA reductasa (estatinas, por ejemplo pravastatina); agonistas PPAR α (fibratos, por ejemplo gemfibrozil); secuestrantes de ácido biliar (colestiramina); inhibidores de absorción de colesterol (estanoles vegetales, inhibidores sintéticos); inhibidores de absorción de ácido biliar (IBATi) y ácido nicotínico y análogos (niacina y formulaciones de liberación lenta);

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- 9) Agentes antihipertensivos tales como, bloqueadores β (por ejemplo atenolol, inderal); inhibidores de la enzima convertidora de la angiotensina (ACE) (por ejemplo lisinopril); antagonistas de calcio (por ejemplo nifedipina); antagonistas de receptor de angiotensina (por ejemplo candesartán), α antagonistas y agentes diuréticos (por ejemplo furosemida, benzotiazida);
- 10) Moduladores de hemostasis tales como, antitrombóticos, activadores 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; y
- 11) 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 más adelante y sales, solvatos y pro-fármacos de los mismos.

Un compuesto de la invención, o una sal del mismo, puede prepararse por cualquier proceso conocido por ser aplicable a la preparación de tales compuestos o compuestos relacionados estructuralmente. Tales procesos se ilustran por los siguientes esquemas representativos (Rutas 1 - 18) en los cuales grupos variables tienen cualquiera de los significados definidos por Fórmula (I) a menos que se indique lo contrario. Los grupos funcionales pueden protegerse y desprotegerse empleando 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 and P.G.M. Wuts, "Protective Groups in Organic Síntesis", Second Edition, John Wiley & Sons, New York, 1991.

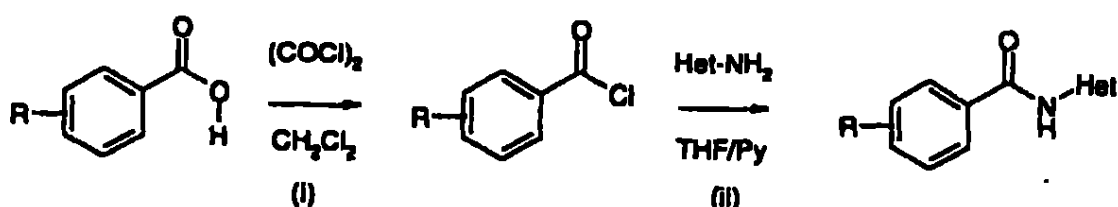
La condensación de un ácido con una amina heterocíclica (Ruta 1) se

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usa en la preparación de compuestos de la invención o en la preparación de intermedios a los productos finales. Entonces pueden realizarse una o más reacciones (tales como hidrólisis de éster, Rutas 2a y 2b) sobre estos intermedios. La reacción formadora de la amida (Ruta 1) se lleva mejor a cabo vía el cloruro de ácido, la cual se prepara usualmente utilizando cloruro de oxalilo. No obstante, pueden emplearse asimismo métodos alternativos para la formación del cloruro de ácido (tal como trifenil fosfina ligada a resina con tetracloruro de carbono y diclorometano). Adicionalmente, pueden usarse métodos alternativos de formación de enlace amida (tal como un agente acoplante peptídico como EDC o HATU, con o sin aditivos tales como DIPEA o DMAP).

Las rutas preparativas restantes (Rutas 2-18) comprenden la manipulación adicional del compuesto con un enlace de amida en su lugar. Otras rutas preparativas se resumen en las Rutas 19-29. Ejemplos de rutas 1-29 se proveen en los ejemplos siguientes. Los reactivos y condiciones dados son únicamente para ilustración y, generalmente, pueden emplearse métodos alternativos.

Ruta 1



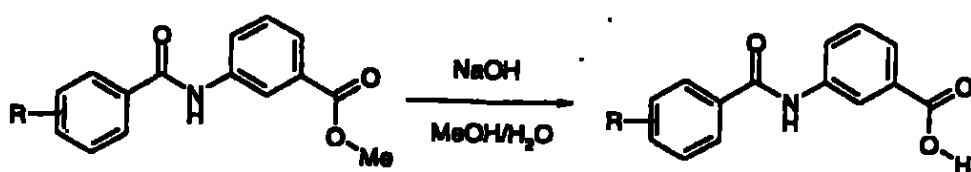
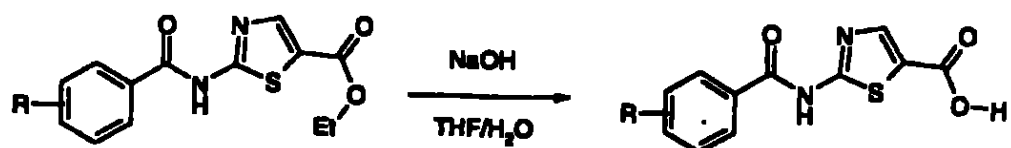
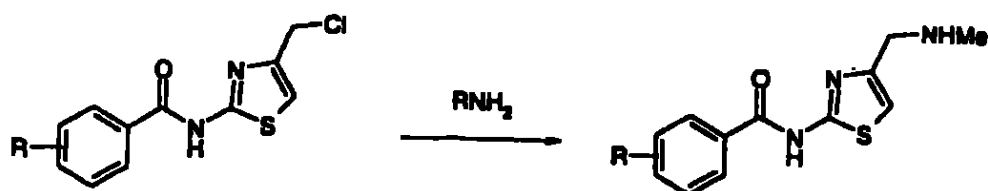
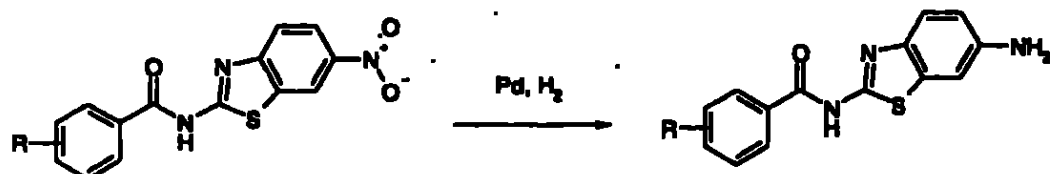
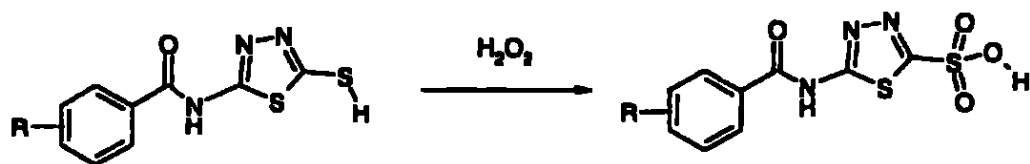
Otras reacciones formadoras de amida comprenden:

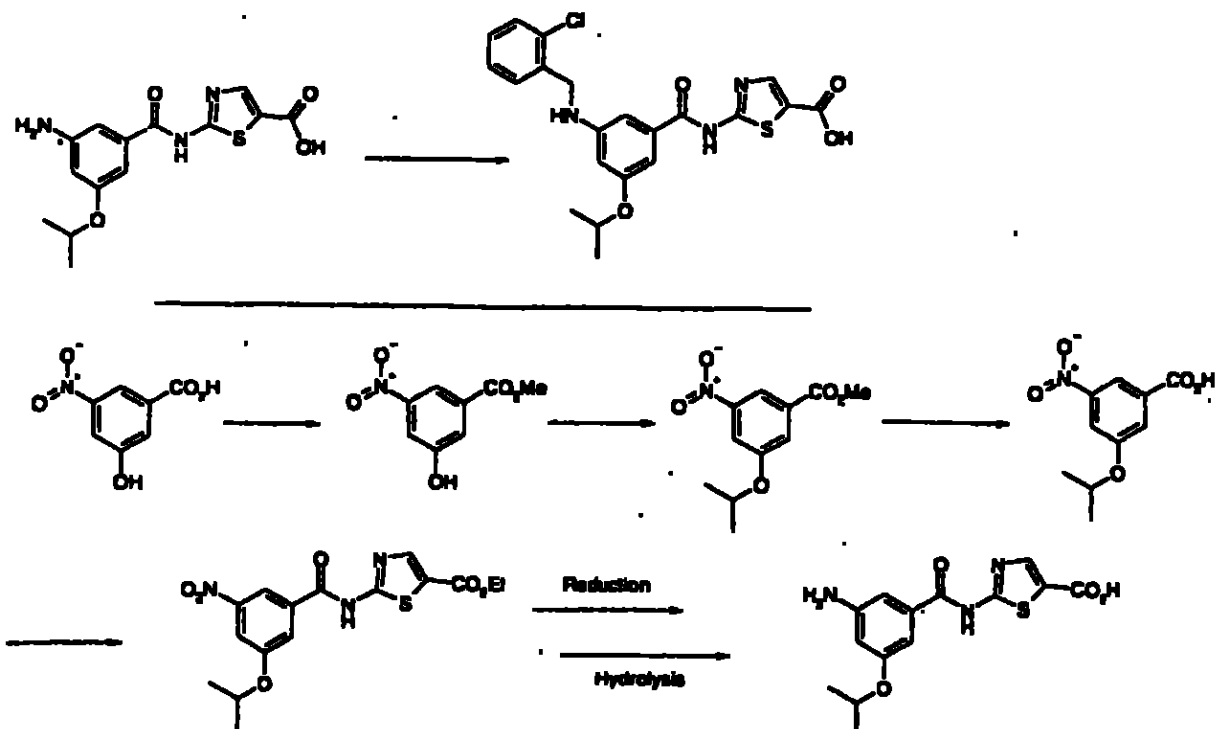
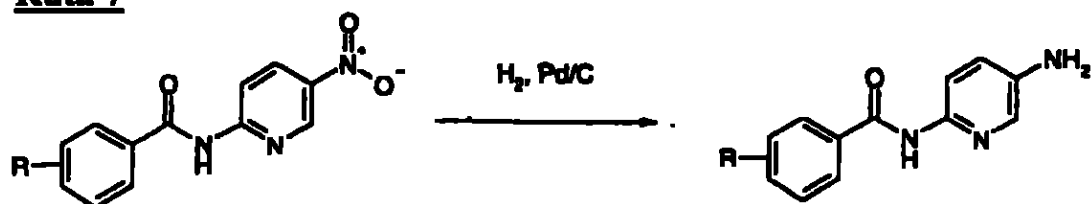
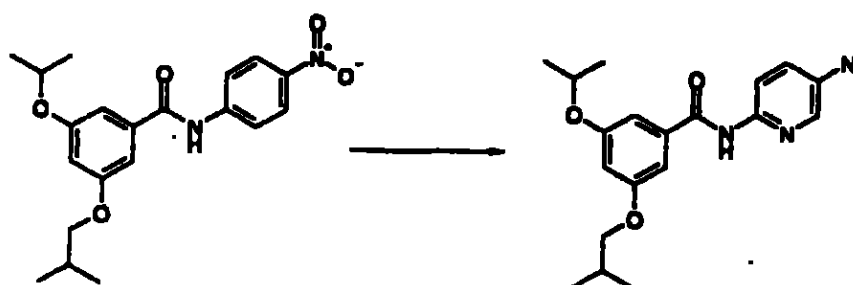
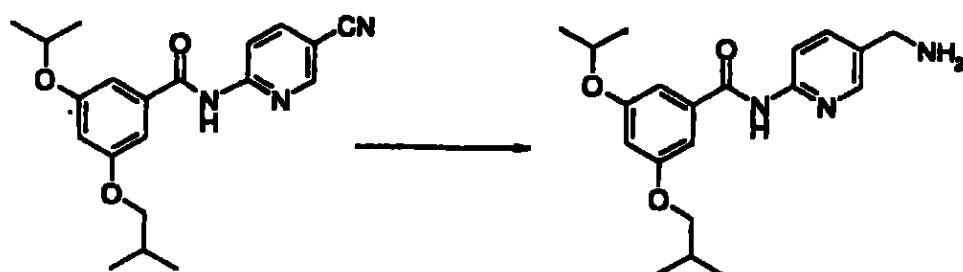
1a: Cloruro de oxalilo en la presencia de un solvente o base adecuados;

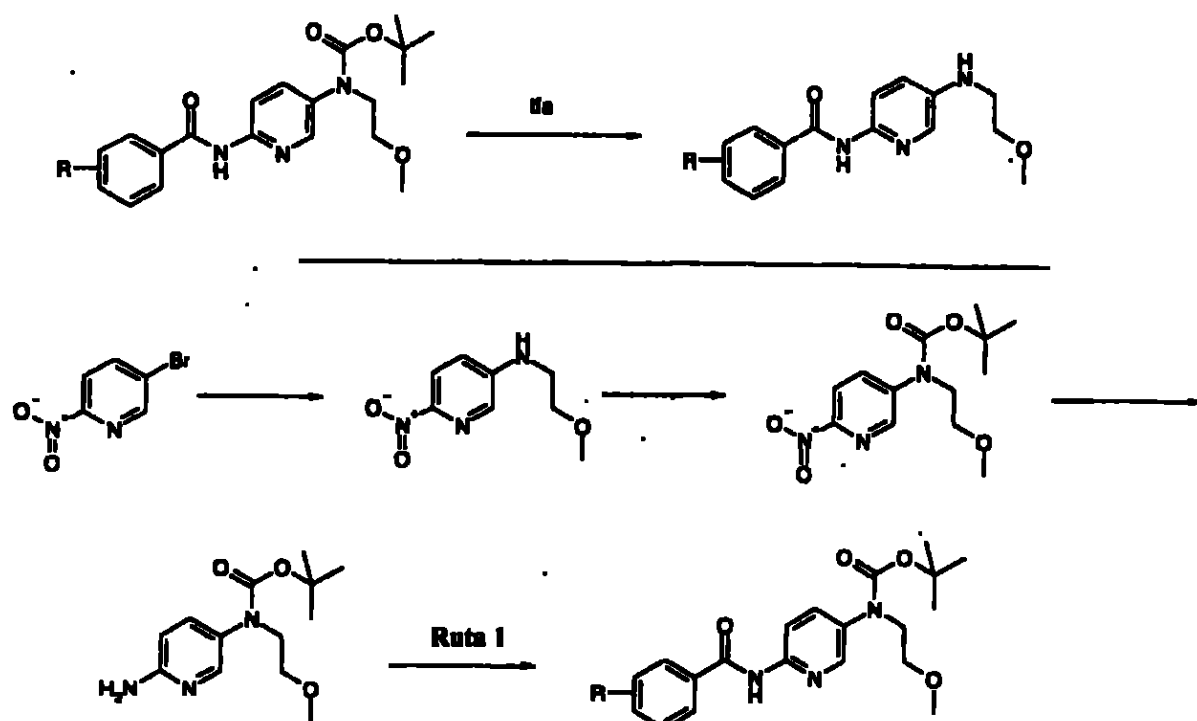
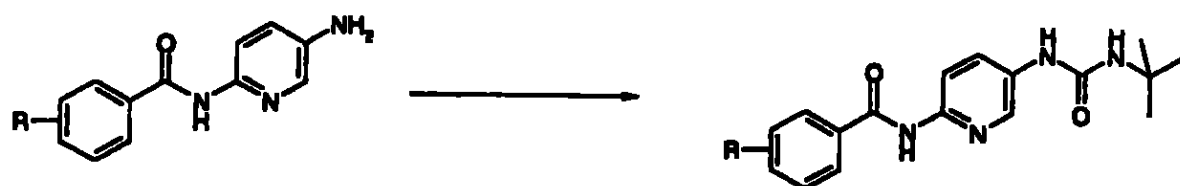
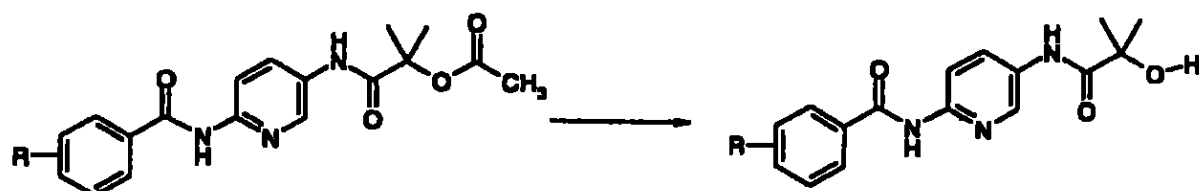
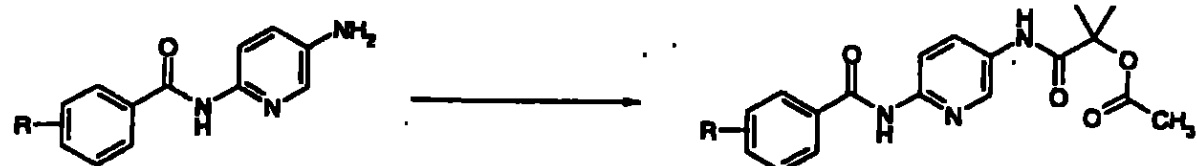
1b: Reactivos de acoplamiento tales como HATU o EDAC en la presencia de un solvente o base adecuados; y

1c: POC13/Piridina, de acuerdo con Dirk T.S. Rijquers, Hans P.H.M. Adams, H. Coenraad Hemquer, Godefridus I. Tesser, Tetrahedron, 1995, 51(41), páginas 11235-11250.

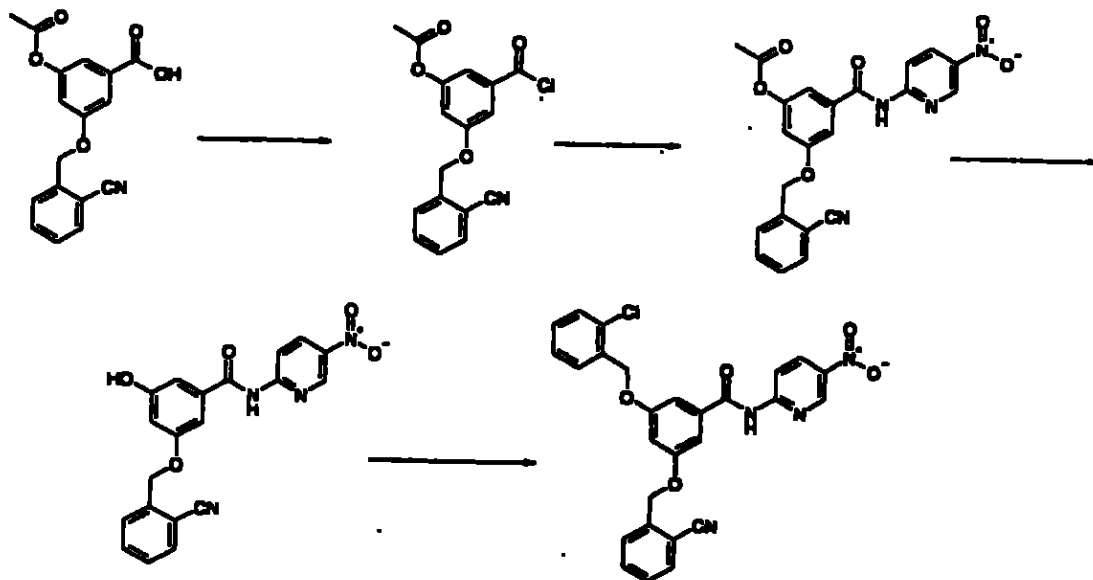
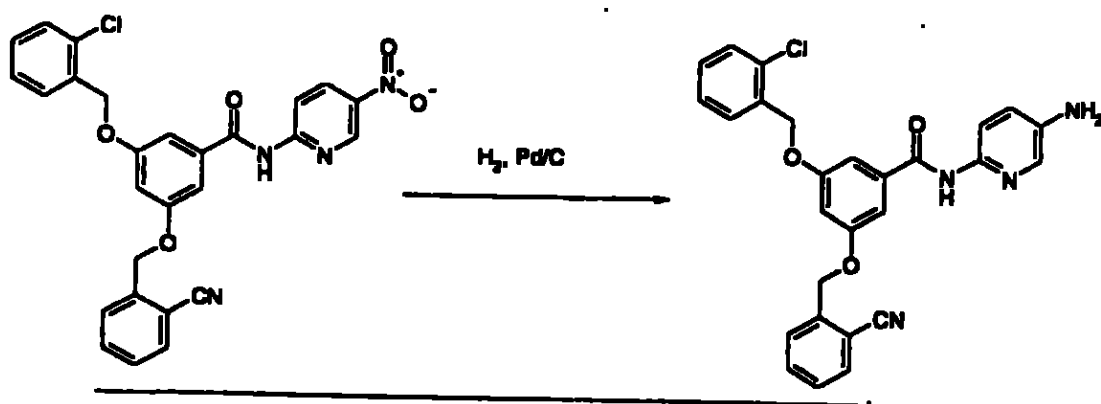
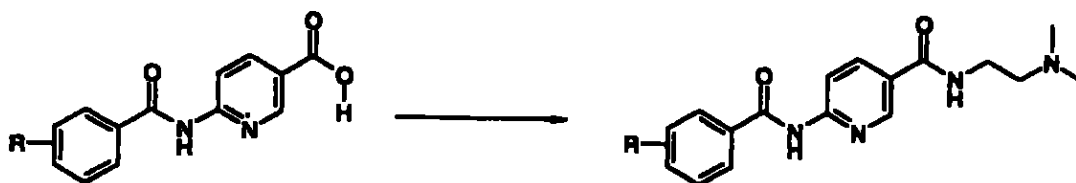
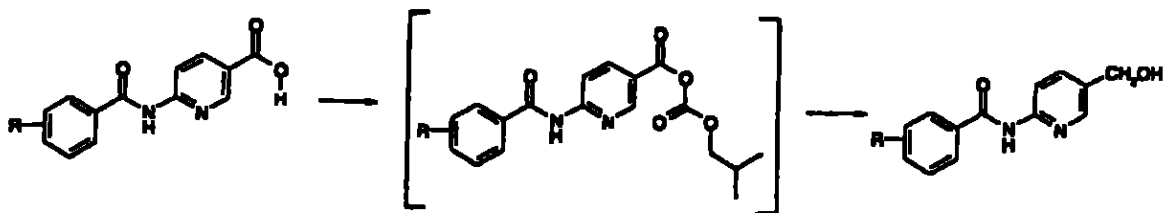
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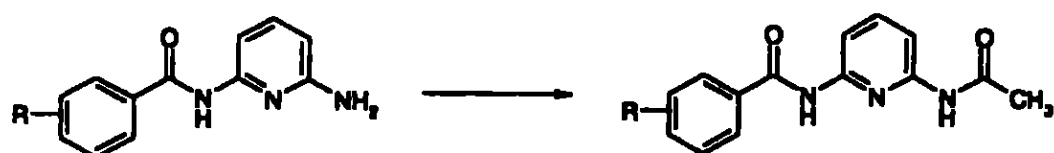
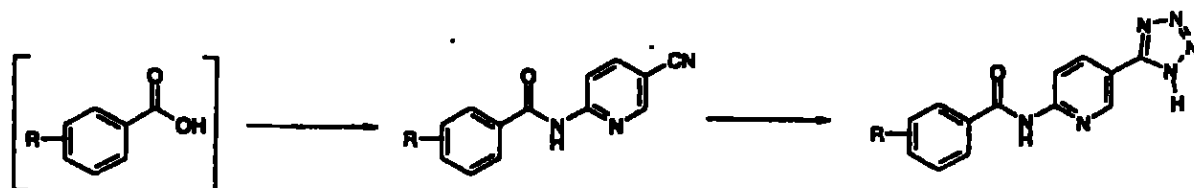
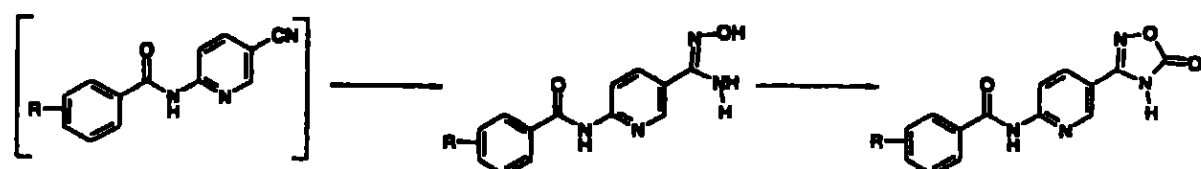
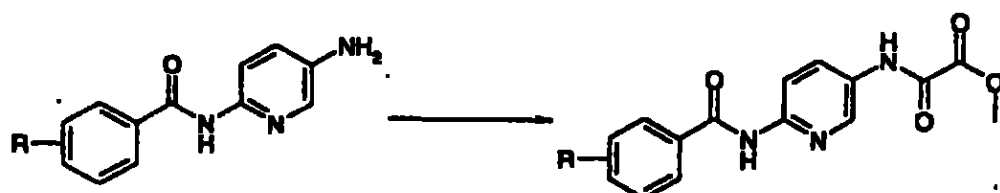
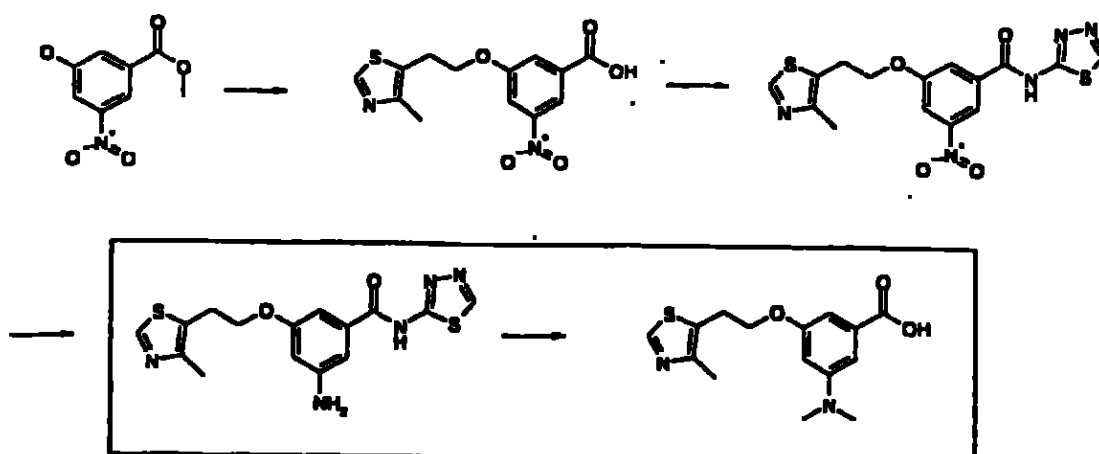
Ruta 2a y 2b**Ruta 3****Ruta 4****Ruta 5**

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+ 2**Ruta 6****Ruta 7****Ruta 7b:****Ruta 7c:**

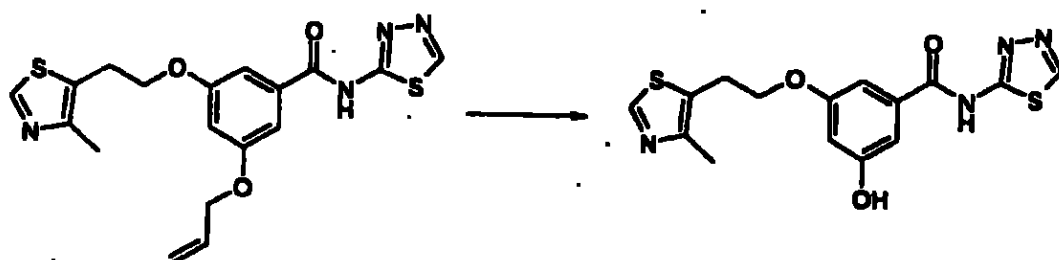
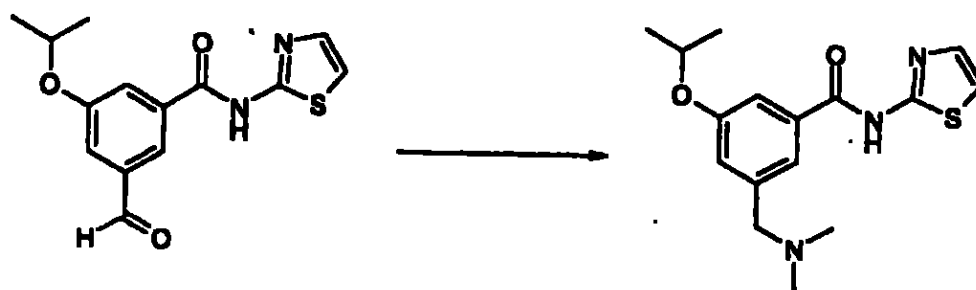
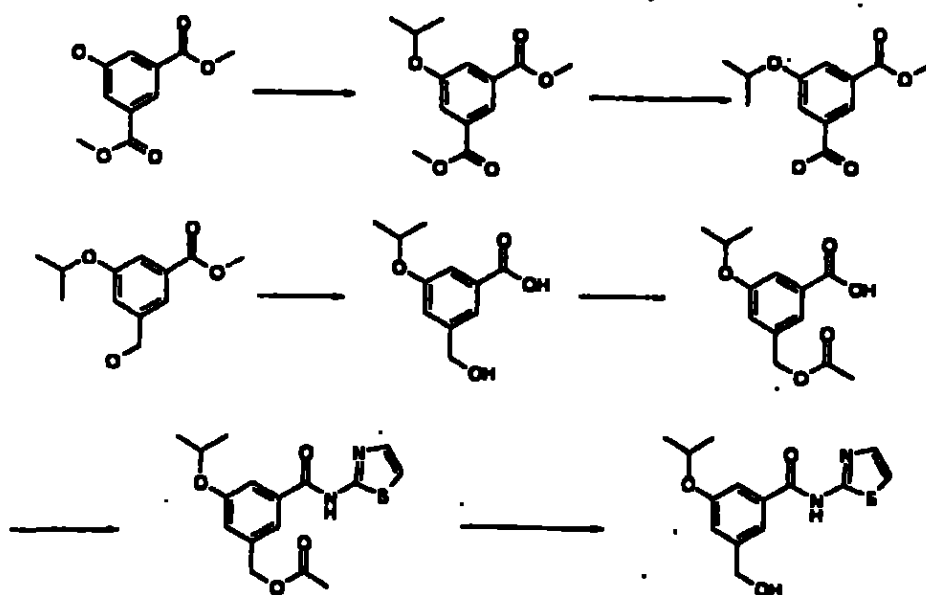


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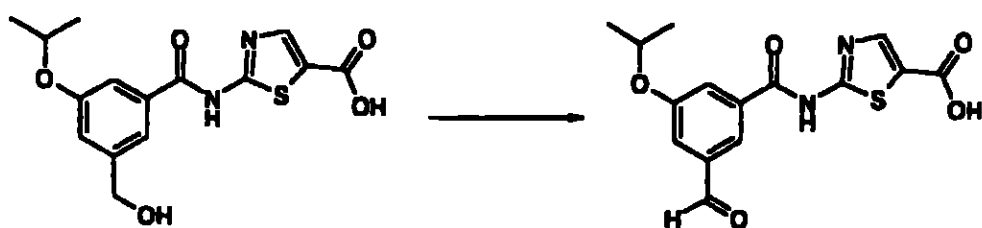
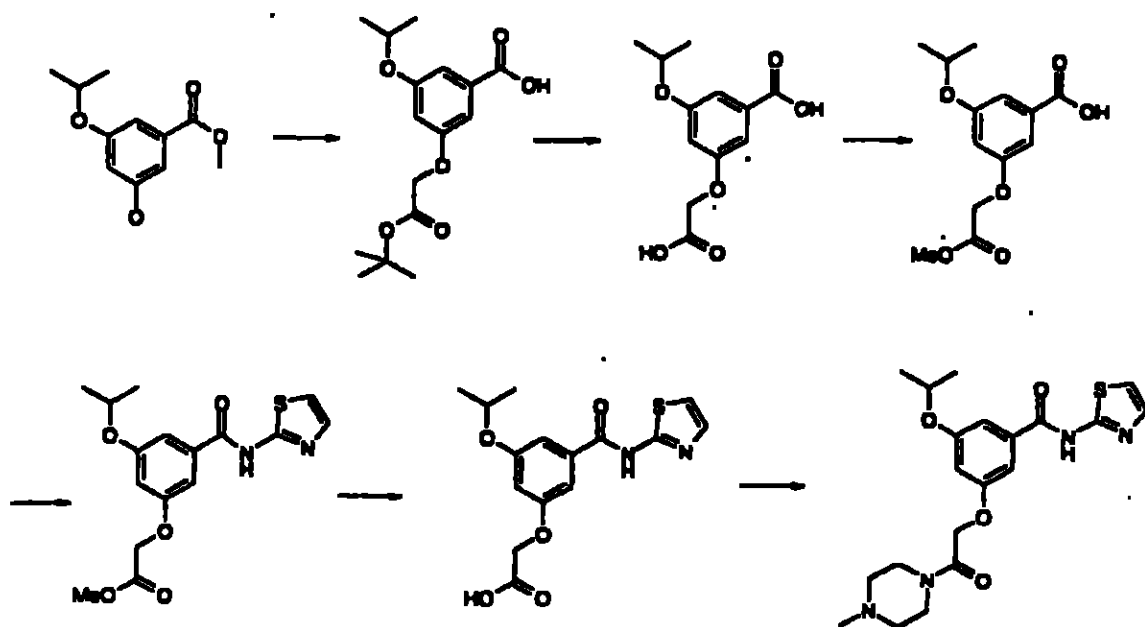
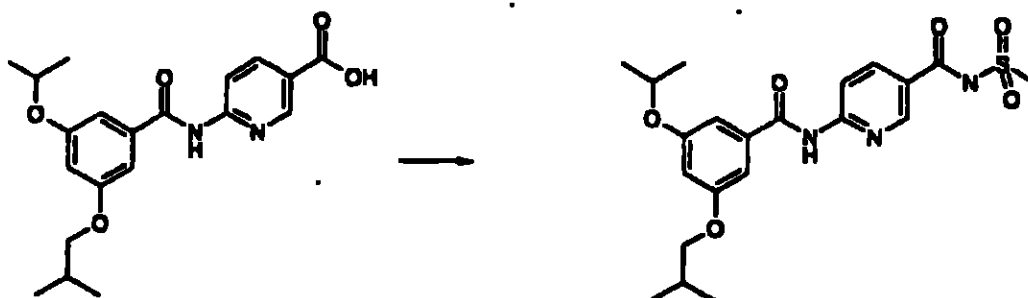
Ruta 12**Ruta 13****Ruta 14**

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f29**Ruta 15****Ruta 16****Ruta 17****Ruta 18****Ruta 19:**

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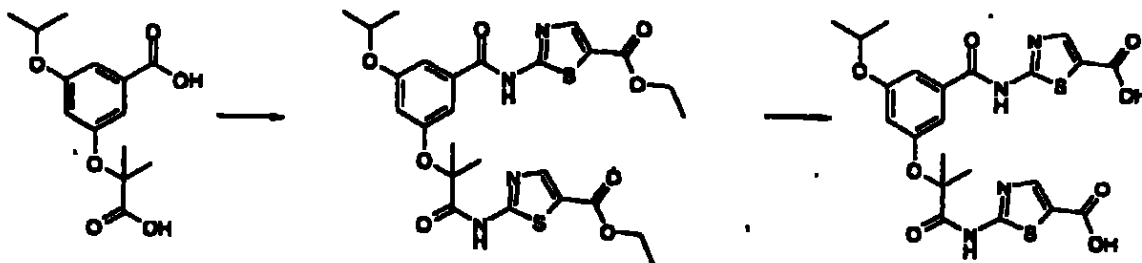
Ruta 20:**Ruta 21:****Ruta 22:****Ruta 23:**

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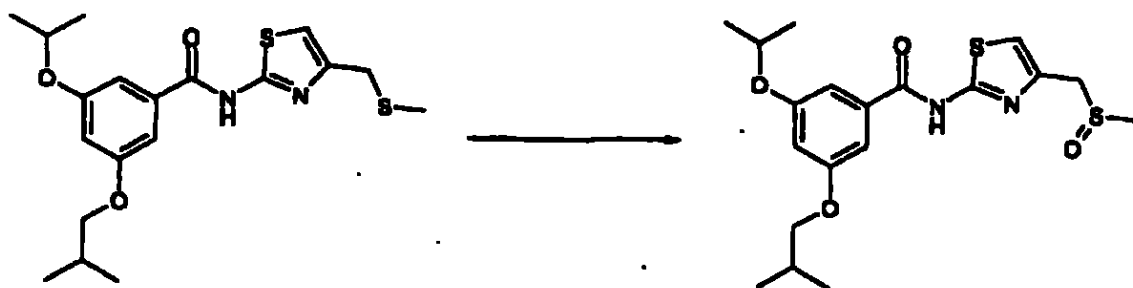
Ruta 24:**Ruta 25:****Ruta 26:****Ruta 27:**

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Ruta 28:

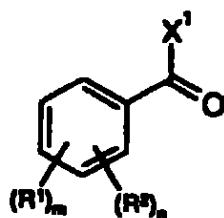


Ruta 29:



Procesos para la síntesis de compuestos de Fórmula (I) se proveen como una característica más de la invención. Así, de acuerdo con un aspecto adicional de la invención se provee un proceso para la preparación de un compuesto de Fórmula (I) que comprende:

- (a) reacción de un compuesto de Fórmula (IIIa) con un compuesto de Fórmula (IIIb),



Fórmula (IIIa)

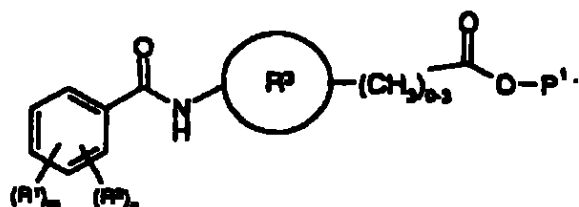


Fórmula (IIIb); o

en donde X¹ es un grupo saliente

- (b) para compuestos de Fórmula (I) en donde R³ se sustituye con - (CH₂)₀₋₃COOH, desprotección de un compuesto de Fórmula (IIIc),

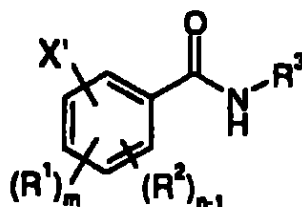
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Fórmula (IIIc)

en donde P¹ es un grupo protector;

- (c) para compuestos de Fórmula (I) en donde n es 1, 2, 3 ó 4, reacción de un compuesto de Fórmula (IIIId) con un compuesto de Fórmula (IIIe),

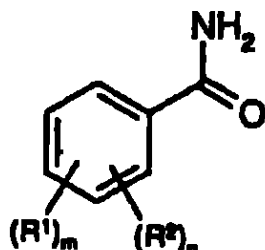


Fórmula (IIIId)

Fórmula (IIIe)

en donde X' y X'' comprenden grupos que cuando se hacen reaccionar juntos forman el grupo X;

- (d) para un compuesto de Fórmula (I) en donde n es 1, 2, 3 ó 4 y X o X¹ es -SO-Z- o -SO₂-Z-, oxidación del correspondiente compuesto de Fórmula (I) en donde X o X¹ respectivamente es -S-Z-;
- (e) reacción de un compuesto de Fórmula (IIIIf) con un compuesto de Fórmula (IIIg),



Fórmula (IIIIf)



Fórmula (IIIg); o

en donde X² es un grupo saliente
y, a partir de entonces, si es necesario:

- i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);

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- ii) retirar los grupos protectores;
- iii) formar una sal, pro-fármaco o solvato del mismo.

Las condiciones de reacción específicas para las reacciones anteriores son como siguen:

Proceso a) – como se describe más arriba para Ruta 1);

Proceso b) – como se describe más arriba para Ruta 2);

Proceso c) - ejemplos de este proceso son los siguientes:

- (i) Para formar un grupo cuando X es -O-Z-, X' es un grupo de Fórmula HO-Z- y X'' es un grupo saliente (alternativamente X' es un grupo de Fórmula L²-Z- en donde L² es un grupo saliente y X'' es un grupo hidroxilo), compuestos de Fórmula (IIIId) y (IIIe) se hacen reaccionar juntos en un solvente apropiado, tal como DMF o THF, con una base tal como hidruro de sodio o *tert*-butóxido de potasio, a una temperatura en el rango de 0 a 100°C, opcionalmente empleando catálisis de metal tal como paladio sobre carbono o yoduro cuproso;
- (ii) Para formar un grupo cuando X es N(R⁶)-Z-, X' es un grupo de Fórmula H-(R⁶)N-Z- y X'' es un grupo saliente (alternativamente X' es un grupo de Fórmula L²-Z- en donde L² es un grupo saliente y X'' es un grupo o Fórmula -N(R⁶)-H), compuestos de Fórmula (IIIId) y (IIIe) se hacen reaccionar juntos en un solvente apropiado tal como THF, un alcohol o acetonitrilo, usando una agente reductor tal como ciano borohidruro de sodio o trisacetoxiborohidruro de sodio a temperatura ambiente;
- (iii) Para formar un grupo cuando X es -SO₂N(R⁶)-Z-, X' es un grupo de Fórmula H-N(R⁶)-Z- en donde L² es un grupo saliente y X'' es un grupo sulfonilo activado tal como un grupo de Fórmula -SO₂-Cl, compuestos de Fórmula (IIIId) y (IIIe) se hacen reaccionar juntos en un solvente apropiado tal como cloruro de metileno, THF o piridina, en la presencia de una base tal como

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triethylamina o piridina a temperatura ambiente;

- (iv) para formar un grupo cuando X es $-N(R^6)SO_2-Z-$, X' es un grupo sulfonilo activado tal como un grupo de Fórmula $Cl-SO_2-Z-$ y X'' es un grupo de Fórmula $-N(R^6)-L^2$ en donde L^2 es un grupo saliente, compuestos de Fórmula (IIId) y (IIle) se hacen reaccionar juntos en un solvente apropiado tal como cloruro de metileno, THF o piridina, en la presencia de una base tal como triethylamina o piridina a temperatura ambiente;
- (v) para formar un grupo cuando X es $-C(O)N(R^6)-Z-$, X' es un grupo de Fórmula $H-N(R^6)-Z-$ en donde L^2 es un grupo saliente y X'' es un grupo carbonilo activado tal como un grupo de Fórmula $-C(O)-Cl$, compuestos de Fórmula (IIId) y (IIle) se hacen reaccionar juntos en un solvente apropiado tal como THF o cloruro de metileno, en la presencia de una base tal como triethylamina o piridina a temperatura ambiente;
- (vi) para formar un grupo cuando X es $-N(R^6)C(O)-Z-$, X' es un grupo carbonilo activado tal como un grupo de Fórmula $Cl-C(O)-Z-$ y X'' es un grupo de Fórmula $-N(R^6)-L^2$ en donde L^2 es un grupo saliente, compuestos de Fórmula (IIId) y (IIle) se hacen reaccionar juntos en un solvente apropiado tal como THF o cloruro de metileno, en la presencia de una base tal como triethylamina o piridina a temperatura ambiente;
- (vii) para formar un grupo cuando X es $-CH=CH-Z-$, puede usarse una reacción Wittig o una reacción Wadsworth-Emmians Horner. Por ejemplo, X' termina en un grupo aldehído y Y-X'' es un derivado de fosfina de la Fórmula $Y-CH-P^+PH_3$ que pueden hacerse reaccionar juntos en una base fuerte tal como hidruro de sodio o *tert*-butóxido de potasio, en un solvente apropiado tal como THF a una temperatura entre temperatura ambiente y 100°C.

Proceso d) - la oxidación de un compuesto de Fórmula (I) en donde X o X¹ es $-S-Z-$ es bien conocida en el arte, por ejemplo, reacción con ácido

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metacloroperbenzoico (MCPBA) en la presencia de un solvente apropiado tal como diclorometano a temperatura ambiente. Si se usa un exceso de MCPBA se obtiene un compuesto de Fórmula (I) en donde X es $-\text{S}(\text{O}_2)-$.

Proceso e) – reacción de una Fórmula (III f) con un compuesto de Fórmula (III g) puede llevarse a cabo en un solvente polar, tal como DMF o un solvente no polar tal como THF con una base fuerte, tal como hidruro de sodio o *tert*-butóxido de potasio a una temperatura entre 0 y 100°C, de manera opcional usando catálisis de metal, tal como paladio sobre carbono o yoduro cuproso.

Durante el proceso de preparación, puede ser conveniente usar un grupo protector para un grupo funcional en R^2 . Grupos protectores pueden retirarse por cualquier método conveniente como se describe en la literatura o conocido por el químico experto como apropiado para el retiro del grupo protector en cuestión, seleccionándose dichos métodos de manera que el retiro del grupo protector se efectúe con una alteración mínima de los grupos en cualquier otra parte de la molécula.

Ejemplos específicos de grupos protectores se indican más adelante por cuestiones de conveniencia, en los cuales "inferior" significa que el grupo, al cual se aplica, tiene preferiblemente 1-4 átomos de carbono. Se entenderá que estos ejemplos no son exhaustivos. Allí donde, más adelante, se dan ejemplos específicos de métodos para el retiro de grupos protectores éstos son igualmente no exhaustivos. El uso de grupos protectores y métodos de desprotección no específicamente mencionado se encuentra, lógicamente, 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 dicho alcohol o silanol preferiblemente 1-20 átomos de carbono). Ejemplos de grupos protectores carboxi comprenden 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,

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pivaloiloximetilo); grupos alquilo inferior alcoxycarbonilo inferior (por ejemplo 1-metoxycarboniloietilo, 1-etoxycarboniloietilo); grupos alquilo inferior arilo (por ejemplo p-metoxibencilo, o-nitrobencilo, p-nitrobencilo, benzhidrido 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)alqueno (por ejemplo alilo y viniletilo).

Métodos particularmente apropiados para el retiro de grupos protectores carboxilo comprenden por ejemplo hidrólisis catalizada por ácido, metal o enzimáticamente.

Ejemplos de grupos protectores hidroxilo comprenden grupos alqueno inferior (por ejemplo alilo); grupos alcanilo inferior (por ejemplo acetilo); grupos alcoxycarbonilo inferior (por ejemplo t-butoxycarbonilo); grupos alquenoiloxycarbonilo inferior (por ejemplo aliloxycarbonilo); grupos alcoxycarbonilo inferior arilo (por ejemplo benzoiloxycarbonilo, p-metoxibenciloxycarbonilo, o-nitrobenciloxycarbonilo, p-nitrobenciloxycarbonilo); grupos trialquilo/arilsililo inferior (por ejemplo trimetilsililo, t-butildimetilsililo, t-butildifenilsililo); grupos alquilo inferior arilo (por ejemplo bencilo); y grupos alquilo inferior triarilo (por ejemplo trifenilmetilo).

Ejemplos de grupos protectores amino comprenden formilo, grupos aralquilo (por ejemplo bencilo y bencilo sustituido, por ejemplo p-metoxibencilo, nitrobencilo y 2,4-dimetoxibencilo, y trifenilmetilo); grupos di-p-anisilmetilo y furilmetilo; grupos alcoxycarbonilo inferior (por ejemplo t-butoxycarbonilo); alquenoiloxycarbonilo inferior (por ejemplo aliloxycarbonilo); grupos alcoxycarbonilo inferior (por ejemplo benciloxycarbonilo, p-metoxibenciloxycarbonilo, o-nitrobenciloxycarbonilo, p-nitrobenciloxycarbonilo); trialquilsililo (por ejemplo trimetilsililo y t-butildimetilsililo); grupos alquilideno (por ejemplo metilideno); bencilideno y bencilideno sustituido.

Métodos apropiados para el retiro de grupos protectores hidroxilo y amino comprenden, por ejemplo, hidrólisis catalizada por ácido, base,

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metal o enzimáticamente, o fotolíticamente para grupos tales como o-nitrobenciloxycarbonilo, o con iones de fluoruro para grupos sililo.

Ejemplos de grupos protectores para grupos amida comprenden 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 tri alquil/sililoximetilo pueden introducirse haciendo reaccionar la amida con el cloruro apropiado y retirando con ácido; o en el caso de los grupos que contienen sililo, iones de fluoruro. Los grupos alcoxifenilo y alcoxibencilo se introducen convenientemente por arilación o alquilación con un halogenuro apropiado y se retiran por oxidación con nitrato de amonio cérico. Finalmente los grupos alqu-1-enilo pueden introducirse haciendo reaccionar la amida con el aldehído apropiado y retirarse con ácido.

Los siguientes ejemplos son con fines de ilustración y no pretenden limitar el alcance 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 indique lo contrario:

(i) las evaporaciones se llevaron a cabo por evaporación rotatoria *in vacuo* y procedimientos de desarrollo se realizaron después del retiro de sólidos residuales como agentes de secamiento por filtración;

(ii) las operaciones se efectuaron a temperatura ambiente, es decir, en el rango de 18-25°C y bajo una atmósfera de un gas inerte tal como

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argón o nitrógeno;

(iii) los rendimientos se dan con fines de ilustración únicamente y no son necesariamente el máximo alcanzable;

(iv) las estructuras de los productos finales de la Fórmula (I) se confirmaron por resonancia magnética nuclear (generalmente de protones) (NMR) y técnicas espectrales de masa; los valores de cambio químico con resonancia magnética de protones se midieron en la escala delta y los múltiplos pico se muestran como sigue: s, singlete; d, doblete; t, triplete; m, multiplete; br; amplio; q, quarteto, quin, quinteto;

(v) por lo general los intermedios no se caracterizado completamente y la pureza se evaluó por cromatografía de capa delgada (TLC), cromatografía líquida de alto rendimiento (HPLC), infra-rojo (IR) o análisis NMR;

(vi) la cromatografía se llevó a cabo en sílice (Merck Silica gel 60, 0.040 - 0.063 mm, 230 - 400 malla); y

(vi) los cartuchos Biotage se refieren a cartuchos de sílice pre-empacados (de 40g hasta 400g), eluidos usando una bomba biotage y sistema colector de fracciones; Biotage UK Ltd, Hertford, Herts, UK.

Abreviaturas

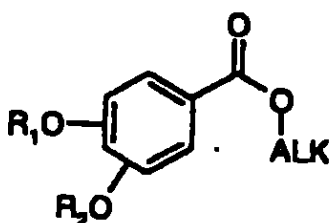
ADDP	azodicarbonil)dipiperidina;
DCM	diclorometano;
DEAD	dietildiazocarboxilato;
DIAD	di-i-propil azodicarboxilato;
DIPEA	di-isopropietilamina
DMSO	sulfóxido de dimetilo;
DMF	dimetilformamida;
DtAD	di-t-butil azodicarboxilato;
EDAC/EDC	1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato;

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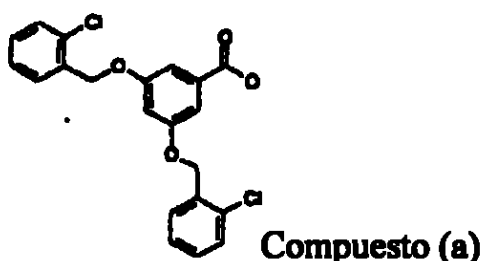
HATU	O-(7-azabenzotriazo-1-il)-N,N,N',N'- tetrametiluronio hexafluorofosfato;
LCMS	cromatografía líquida / espectroscopía de masa;
MPLC	cromatografía líquida de presión media;
RT	temperatura ambiente; y
THF	tetrahidrofurano.

Métodos genéricos para la alquilación de ésteres de mono- y di-hidroxibenzoato:

Los siguientes métodos genéricos de alquilación se mencionan en los Ejemplos que siguen.



Método Genérico A – síntesis de diéteres simétricos (R1 = R2)



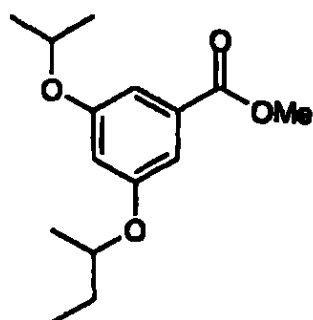
Compuesto (a)

Metil 3,5-dihidroxibenzoato (74.1g, 0.44M) se disolvió en dimetilformamida (400ml), se agregó carbonato de potasio (152g, 1.10M), se agitó durante 15 minutos, luego se adicionó 2-clorobencilcloruro (117ml, 0.92M) y se calentó a 100°C bajo una atmósfera de argón. Después de 3 horas la mezcla de reacción se enfrió a temperatura ambiente, se concentró *in vacuo*, se diluyó con agua (800ml), se extrajo con acetato de etilo (2x600ml). Los extractos orgánicos se lavaron con salmuera (300ml), se secaron (MgSO₄), se filtraron, se concentraron *in vacuo* para producir un aceite marrón el cual se trituroó con éter dietílico / isohexano para producir compuesto (a) como un sólido blancuzco (195g, 100%); ¹H nmr (d6-

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DMSO, valores δ): 3.81 (3H, s); 5.18 (4H, s); 6.98 (1H, m); 7.16 (1H, d); 7.36 (4H, m); 7.50 (2H, m); 7.58 (2H, m).

Método Genérico B – síntesis de diéteres asimétricos (R1 = R2)



Compuesto (b)

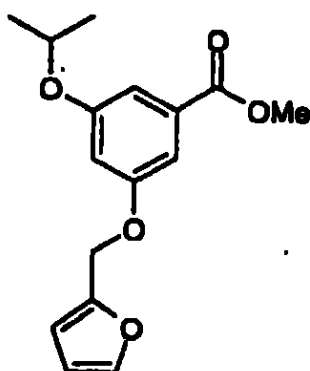
Metil 3,5-dihidroxibenzoato (16.8g, 0.1mol) se disolvió en dimetilformamida (180ml), se agregó carbonato de potasio pulverizado (27.6 g, 0.2mol), seguido por 2-yodopropano (10ml, 0.1mol), y la suspensión resultante se agitó durante la noche a temperatura ambiente bajo una atmósfera de argón. La mezcla de reacción se diluyó con agua (1l) y se extrajo con éter dietílico (2x200ml). Los extractos orgánicos se lavaron secuencialmente con agua y salmuera, se secaron (MgSO_4), se filtraron y se concentraron *in vacuo* para producir un aceite dorado amarillo el cual se trituró con tolueno y se filtró para retirar el material inicial éter sin reaccionar. El filtrado se concentró *in vacuo* y el residuo se cromatografió (cartuchos Biotage 2x90 g, eluyendo con isohexano que contenía acetato de etilo (10% v/v aumentando a 15% v/v) para producir metil 3-hidroxi 5-isopropiloxi benzoato como un sólido incoloro (5.3g, 25%); ^1H nmr (d_6 -DMSO, valores δ): 1.2 (6H, d); 3.8 (3H, s); 4.6 (1H, hept); 6.55 (1H, m); 6.85 (1H, m); 6.95 (1H, m); 9.8 (1H, s).

Metil 3-hidroxi 5-isopropiloxi benzoato (1.5g, 7.2mmol) se disolvió en dimetilformamida (10ml), se agregó carbonato de potasio (2.5g, 18mmol), seguido por 2-bromobutano (1.2 ml, 11mmol), y la suspensión resultante se agitó durante 7 horas a 80 °C bajo una atmósfera de argón. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con hexano / acetato de etilo (1:1 v/v) y se lavó secuencialmente con agua y salmuera, se secó

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(MgSO₄), se filtró y se concentró *in vacuo* para producir un aceite incoloro el cual se cromatografió (columna de destello en sílice (20g), eluyendo con isohehexano que contenía acetato de etilo (5 % v/v) para producir metil 3-(2-butiloxi) 5-isopropiloxi benzoato como un aceite incoloro (1.06g); ¹H nmr (d6-DMSO, valores δ): 0.9 (3H, t); 1.2 (3H, d + 6H, d); 1.6 (2h, m); 3.85 (3H, s); 4.4 (1H, hept); 4.55 (1H, hept); 6.7 (1H, m); 7.0 (2H, m); m/z 267 (M+H)+.

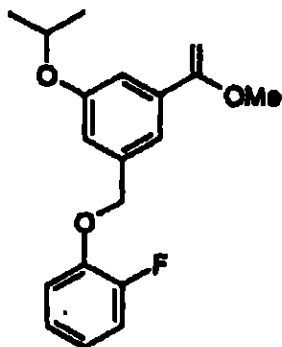
Método Genérico C – síntesis de diéteres asimétricos (R1 = R2):



Compuesto (c)

Metil 3-hidroxi 5-isopropiloxi benzoato (0.5g, 2.4mmol) se disolvió en diclorometano (10ml) y se enfrió a 0 °C agitando al mismo tiempo bajo una atmósfera de argón; la solución se trató secuencialmente con trifenil fosfina (con soporte polimérico, 1.19g, 3.6mmol), alcohol furfurílico (0.23 ml, 2.7 mmol) y di-t-butil azodicarboxilato (DtAD, 0.082g, 3.5 mmol) se agregaron gota a gota en diclorometano (4ml), y la solución resultante se agitó durante 1.5 horas. La reacción se monitoreó por hplc y se agregaron reactivos adicionales hasta que se consumió el fenol inicial – los reactivos totales fueron trifenil fosfina (con soporte polimérico, 2.38g, 3 eq), alcohol furfurílico (0.53 ml, 2.5 eq) y DtAD (1.64g, 3 eq). La mezcla de reacción se concentró *in vacuo* y se purificó por cromatografía (columna de destello en sílice, eluyendo con isohehexano que contenía acetato de etilo (5 % v/v) para producir metil 3-(2-furil metoxi) 5-isopropiloxi benzoato como un aceite incoloro, (0.225g); ¹H nmr (d6-DMSO, valores δ): 1.25 (6H, d); 3.85 (3H, s); 4.65 (1H, hept); 5.1 (2H, s); 6.45 (1H, m); 6.6 (1H, m); 6.85 (1H, m); 7.05 (1H, m); 7.15 (1H, m) 7.75 (1H, m).

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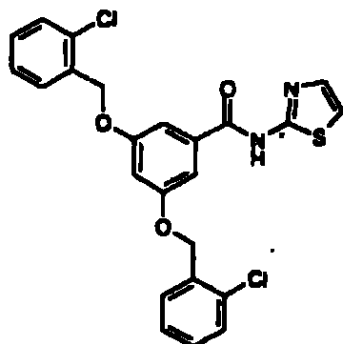
Método Genérico D - síntesis de diéteres asimétricos:**Compuesto (d)**

Di-i-propil azodicarboxilato (DIAD, 0.74ml, 3.7 mM) se agregó a metil (5-isopropoxi-3-metanol)-benzoato (0.56g, 2.5 mM), trifenilfosfina (0.98g, 3.7 mM) y 2-fluorofenol (0.24ml, 2.7 mM) en DCM (40ml) bajo argón a temperatura ambiente. Después de 10 minutos se concentraron, se purificaron en gel de sílice (10-15%EtOAc/iso-hexano) y produjeron el compuesto del título como un aceite amarillo pálido; que se solidificó bajo alto vacío (0.71 g, 90%); ^1H NMR δ (d_6 -DMSO); 1.26 (d, 6H), 3.82 (s, 3H), 4.64 (m, 1H), 5.21 (s, 2H), 6.92 (m, 1H), 7.09 (m, 1H), 7.16-7.26 (m, 3H), 7.35 (s, 1H), 7.58 (s, 1H).

Los anteriores métodos genéricos son para ilustración únicamente; se apreciará que condiciones que pueden utilizarse adicionalmente comprenden: uso de solventes alternativos (tales como acetona o tetrahidrofurano), estequiometrías alternativas de reactivos, temperaturas alternativas de reacción y métodos alternativos de purificación.

Todos los datos analíticos (NMR y/o MS) fueron consistentes con las estructuras propuestas.

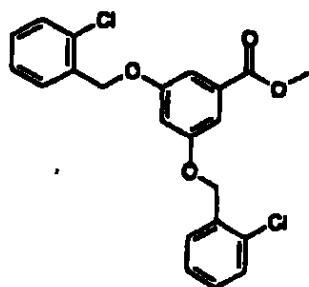
EJEMPLO A**Ruta 1: 2-[3,5-Di-(2-clorobenciloxi)benzoil)amino]-tiazol**

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Diisopropiletilamina (DIPEA, 0.34ml, 2.0mM) luego N,N-dimetilaminopiridina (DMAP, 12mg, 0.1mM) se agregaron a una solución de 2-aminotiazol (0.10g, 1.0mM) y cloruro de ácido 3,5-di-(2-clorobenciloxi) benzoico (0.42g, 1.0mM) en diclorometano (10ml) bajo argón a temperatura ambiente. Luego de 80 minutos la mezcla de reacción se filtró, se lavó con diclorometano y se secó bajo alto vacío para producir el compuesto del título como un sólido incoloro (0.20g, 41%); ^1H NMR δ (d_6 -DMSO): 5.24 (4H, s); 6.93 (1H, s); 7.26 (1H, d); 7.36-7.43 (6H, m); 7.50 (2H, m); 7.55 (1H, d); 7.61 (2H, m); 12.60 (1H, br s).

Condiciones alternativas que pueden usarse opcionalmente comprenden: uso de un solvente alternativo, tal como tetrahidrofurano; uso de piridina como solvente, con o sin la adición de DMAP o DIPEA; disolver el componente cloruro de ácido en el solvente de elección, y agregarle el componente amina.

El material inicial requerido ácido 3,5-di-(2-clorobenciloxi) benzoico, compuesto (c), se preparó como sigue:

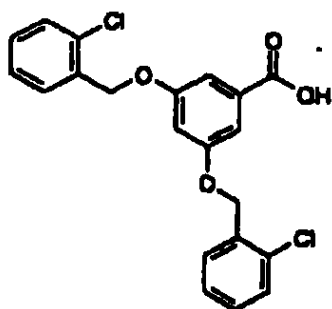


Compuesto (a)

Metil 3,5-dihidroxibenzoato (74.1g, 0.44M) se disolvió en

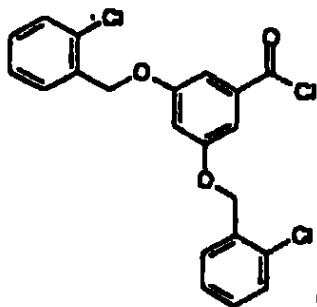
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dimetilformamida (400ml), se agregó carbonato de potasio (152g, 1.10M), se agitó durante 15 minutos, luego se agregó 2-clorobencilcloruro (117ml, 0.92M) y se calentó a 100°C bajo una atmósfera de argón. Después de 3 horas la mezcla de reacción se enfrió a temperatura ambiente, se concentró *in vacuo*, se diluyó con agua (800ml), se extrajo con acetato de etilo (2x600ml). Los extractos orgánicos se lavaron con salmuera (300ml), se secaron (MgSO₄), se filtraron, se concentraron *in vacuo* para producir un aceite marrón que se trituró con éter dietílico / isohexano para producir compuesto (a) como un sólido blancuzco (195g, 100%); ¹H nmr (d₆-DMSO, valores δ): 3.81 (3H, s); 5.18 (4H, s); 6.98 (1H, m); 7.16 (1H, d); 7.36 (4H, m); 7.50 (2H, m); 7.58 (2H, m).



Compuesto (b)

2M hidróxido de sodio (700ml, 1.40M) se agregó a una solución de compuesto (a), metil 3,5-di-(2-clorobenciloxi) benzoato, (195g, 0.45M) en metanol (600ml)/ tetrahidrofurano (150ml) y se agitó durante 6 horas a 55°C. Los orgánicos se retiraron entonces *in vacuo*, se acidificaron a pH 3-4 con ácido clorhídrico concentrado, el precipitado se filtró, se lavó con agua y se secó bajo alto vacío a 60°C. Compuesto (b) se obtuvo como un sólido incoloro (.2/3NaCl) (199g, 100%); ¹H nmr (d₆-DMSO, valores δ): 5.18 (4H, s); 6.93 (1H, m); 7.15 (1H, d); 7.37 (4H, m); 7.49 (2H, m); 7.58 (2H, m).



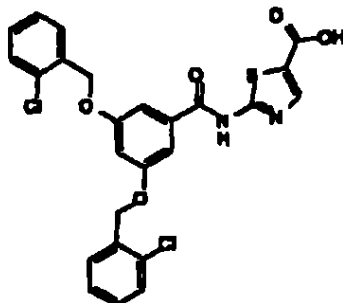
Compuesto (c)

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Cloruro de oxalilo (7.91ml, 91mM) se agregó a una suspensión de compuesto (b), ácido 3,5-di-(2-clorobenciloxi) benzoico, 2/3NaCl (18.3g, 45.4mM) en diclorometano (500ml) que contenía dimetilformamida (4 gotas) bajo argón a temperatura ambiente. Después de 16 horas la mezcla de reacción se filtró bajo argón, se concentró *in vacuo*, luego se sometió a destilación bajo temperatura fija con tolueno (2x) para producir el compuesto del título como un sólido blancuzco (17.5g, 100%); ^1H nmr ($\text{d}_6\text{-DMSO}$, valores δ): 5.18 (4H, s); 6.94 (1H, m); 7.16 (1H, d); 7.35 (4H, m); 7.50 (2H, m); 7.58 (2H, m).

EJEMPLO B

Ruta 2a: ácido 2-[3,5-di-(2-clorobenciloxi)benzoil]aminotiazol-5-carboxílico



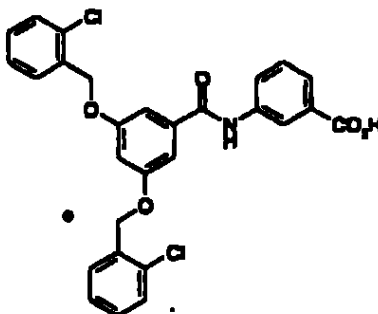
Una solución de 2-[3,5-di-(2-clorobenciloxi)benzoil]aminotiazol-5-carboxilato de etilo (158mg, 0.28 mmol) en THF (2 ml) se trató con solución de hidróxido de sodio (0.57 ml of 2M, 1.4 mmol), y la reacción se agitó a 40 - 50 °C, hasta que se consiguió una hidrólisis completa (con monitoreo de tlc, tiempo aproximado de reacción 2 horas). La solución resultante se enfrió, se diluyó con agua (5 ml) y se acidificó a pH 1 usando c.HCl. El precipitado así formado se extrajo por filtración, se lavó (agua) y se secó para producir el compuesto del título como un sólido incoloro, 130mg, ^1H NMR δ ($\text{d}_6\text{-DMSO}$): 5.25 (4H, s); 7.0 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.2 (1H, d).

El material inicial requerido se preparó por una ruta análoga a la dada Ejemplo A.

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EJEMPLO C

Ruta 2b: ácido [3,5-di-(2-clorobenciloxi)benzoil]aminobencen-3-carboxílico

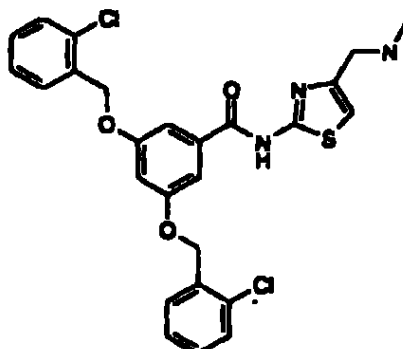


Una suspensión de [3,5-di-(2-clorobenciloxi)benzoil]aminobencen-3-carboxilato de metilo (455mg, 1.04 mmol) en THF se trató con solución de hidróxido de sodio (0.85 ml ó 2M, 1.7 mmol), y la reacción se agitó a temperatura ambiente, con monitoreo de tlc. Se realizaron adiciones de metanol (3 gotas) y otras adiciones de solución de hidróxido de sodio (2 x 0.85 ml of 2M, 3.4 mmol), hasta que se consiguió una hidrólisis completa. La solución resultante se diluyó con agua (30 ml) y se acidificó a pH 1 (2M HCl); el precipitado así formado se extrajo por filtración, se lavó (agua) y se secó para producir el compuesto del título como un sólido incoloro, 328mg, ¹H NMR δ (d₆-DMSO): 5.25 (4H, s); 7.0 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.2 (1H, d).

El material inicial requerido ester de metilo se preparó por un método análogo al dado en Ejemplo A.

EJEMPLO D

Ruta 3: 2-[3,5-Di-(2-clorobenciloxi)benzoil]amino-4-metil aminometil tiazol

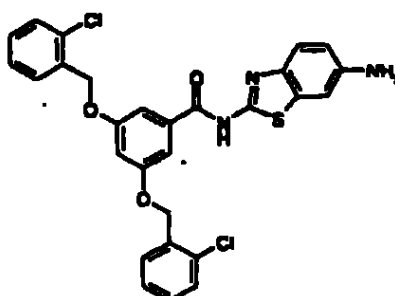
148
F49

2-[3,5-Di-(2-clorobenciloxi)benzoyl]amino]-4-clorometiltiazol (56mg, 0.10mM) se disolvió en 33% metilamina en alcohol metilado (4ml) y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró *in vacuo*, se trituró con metanol, se filtró y se secó bajo alto vacío para producir el compuesto del título como un sólido incoloro (30mg, 57%); ^1H nmr ($\text{d}_6\text{-DMSO}$, valores δ): 2.63 (3H, m); 4.16 (2H, m); 5.24 (4H, s); 6.99 (1H, s); 7.38-7.44 (7H, m); 7.52 (2H, m); 7.62 (2H, m); 9.06 (1H, br s); 12.75 (1H, br s).

2-[3,5-Di-(2-clorobenciloxi)benzoyl]amino]-4-clorometiltiazol se preparó de 3,5-di-(2-clorobenciloxi) benzoyl cloruro (preparado de acuerdo con el método descrito en Ejemplo A) y 2-amino 4-clorometil-tiazol (JACS, 1946, 68, 2155; preparado por ruta 1 descrito en Ejemplo A).

EJEMPLO E

Ruta 4: 2-[3,5-Di-(2-clorobenciloxi)benzoyl]amino]-6-aminobenzotiazol



2-[3,5-Di-(2-clorobenciloxi)benzoyl]amino]-6-nitrobenzotiazol (235mg, 0.40mM) se disolvió en acetato de etilo (40ml), etanol (20ml) y

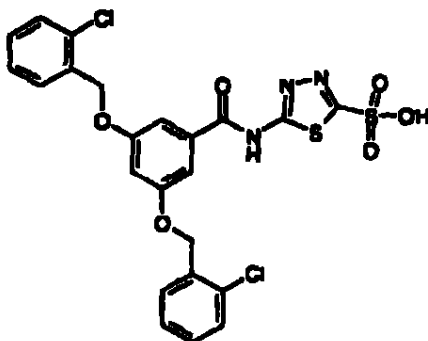
D
129

dimetilformamida (5ml). Se agregó 5% paladio sobre carbono (46mg) bajo una atmósfera de argón, seguidamente la mezcla de reacción se agitó bajo una atmósfera de hidrógeno durante 16 horas. La mezcla de reacción se filtró a través de celita, se concentró *in vacuo*, se trituró con metanol para producir el compuesto del título como un sólido amarillo pálido (140mg, 63%); ¹H nmr (d6-DMSO, valores δ): 5.19 (2H, br s); 5.23 (4H, s); 6.72 (1H, dd); 6.93 (1H, m); 7.03 (1H, m); 7.35-7.44 (7H, m); 7.51 (2H, m); 7.61 (2H, m); 12.46 (1H, br s).

2-[3,5-Di-(2-clorobenciloxi)benzoi]amino]-6-nitrobenzotiazol se preparó de 3,5-di-(2-clorobenciloxi) benzoi] cloruro (preparado de acuerdo con el método descrito en Ejemplo A) y 2-amino-6-nitrobenzotiazol (preparado por ruta 1 descrito en Ejemplo A). ¹H nmr (d6-DMSO, valores δ): 5.27 (4H, s); 7.03 (1H, s); 7.38-7.46 (4H, m); 7.49-7.55 (4H, m) 7.65 (2H, m); 7.93 (1H, d); 8.30 (1H, dd); 9.09 (1H, m); 13.28 (1H, br s).

EJEMPLO F

Ruta 5: ácido 5-[3,5-di-(2-clorobenciloxi)benzoi]amino]-[1,3,4]tiadiazol-2-sulfónico



5-[3,5-Di-(2-clorobenciloxi)benzoi]amino]-[1,3,4]tiadiazol-2-tiol (200mg, 0.38mM) se suspendió en 2M NaOH (5ml), se enfrió (baño helado) y se agregó 30% peróxido de hidrógeno acuoso (0.16ml, 1.54mM) gota a gota, seguidamente se dejó calentar a temperatura ambiente. Después de 40 horas la mezcla de reacción se filtró, se lavó con agua, luego metanol y se secó bajo alto vacío para producir el compuesto del título como un sólido incoloro (122mg, 57%). ¹H nmr (d6-DMSO, valores δ): 5.20 (4H, s); 6.68

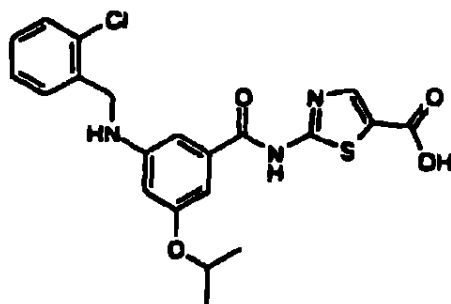
17150

(1H, m); 7.37 (4H, m); 7.45 (2H, m); 7.50 (2H, m); 7.62 (2H, m). MS (M-H⁺)⁻ 564, 566.

5-[3,5-Di-(2-clorobenciloxi)benzoil)amino]-[1,3,4]tiadiazol-2-tiol se preparó de 3,5-di-(2-clorobenciloxi)benzoil cloruro y 5-amino-[1,3,4]tiadiazol-2-tiol (Maybridge) por ruta 1 como se describe en Ejemplo A. ¹H nmr (d₆-DMSO, valores δ): 5.21 (4H, s); 6.98 (1H, m); 7.34-7.40 (6H, m); 7.50 (2H, m); 7.59 (2H, m). MS (M-H⁺)⁻ 516, 518.

EJEMPLO G

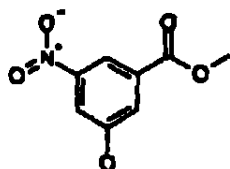
Ruta 6: ácido 2-[(3-isopropiloxi-5-(2-clorobencilamino)benzoil)amino]-5-tiazolcarboxílico



2-Clorobenzaldehído (0.012ml, 0.11mM) se agregó a ácido 2-[(3-isopropoxi-5-aminobenzoil)amino]-5-tiazolcarboxílico (29mg 0.09mM) y mallas moleculares 4A (90mg) en metanol bajo una atmósfera inerte a temperatura ambiente. Después de 1 hora se adicionó cianoborohidruro de sodio (7mg, 0.11mM) y la mezcla de reacción se agitó durante 16 horas. La mezcla de reacción se filtró, se concentró *in vacuo*, el residuo se agitó con agua, seguidamente se extrajo con acetato de etilo (3x10ml). Los extractos orgánicos se lavaron con salmuera (20ml), se secaron (MgSO₄), se filtraron y se concentraron *in vacuo* para producir el compuesto del título como un sólido amarillo pálido (22mg, 55%); ¹H nmr (d₆-DMSO, valores δ): 1.22 (6H, d); 4.36 (2H, m); 4.58 (1H, m); 6.24 (1H, s); 6.47 (1H, m); 6.84 (2H, m); 7.26 (3H, m); 7.37 (2H, m); 7.45 (1H, m); 7.76 (1H, br s). MS [M-CO₂H]⁻ 400, 402.

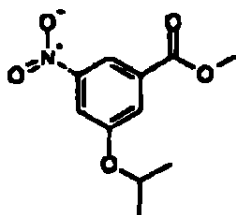
151

Ácido 2-[(3-isopropiloxi-5-aminobenzoil)amino]-5-tiazolcarboxílico se preparó como sigue:



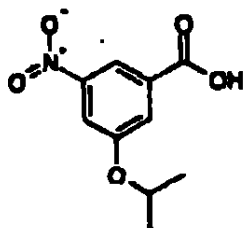
Compuesto (d)

Ácido 3-nitro-5-hidroxi benzoico (6.1g, 33.3mM) se disolvió en metanol (150ml.), se agregó ácido sulfúrico (2.0ml), y la solución se agitó a temperatura ambiente durante 5 días. La mezcla de reacción se concentró *in vacuo*, se agregó cuidadosamente carbonato hidrogenado de sodio acuoso saturado (60ml) y se extrajo la capa acuosa con acetato de etilo (200ml). La capa orgánica se lavó con salmuera (80ml), se secó (MgSO₄), se filtró y se concentró *in vacuo* para producir compuesto (d) como un sólido amarillo pálido (6.0g, 91%); ¹H nmr (d₆-DMSO, valores δ): 3.85 (3H, s); 7.67 (1H, m); 7.75 (1H, m); 8.05 (1H, m); 10.88 (1H, br s).



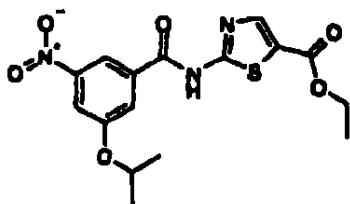
Compuesto (e)

2-yodopropano (0.54ml, 5.4mM) se agregó a una solución de metil 3-nitro-5-hidroxi benzoato (1.06g, 5.4mM) y carbonato de potasio (1.12g, 8.1mM) en dimetilformamida (15ml) bajo una atmósfera de argón a temperatura ambiente. La mezcla de reacción se calentó a 60°C durante 1 hora; seguidamente se agregó más 2-yodopropano (0.32ml, 3.2mM) y el calentamiento se continuó durante 1 hora más. Entonces la mezcla de reacción se concentró *in vacuo*, se agregó agua (50ml) y acetato de etilo (100ml). La capa orgánica se separó y se lavó con salmuera (40ml), se secó (MgSO₄) se filtró, se concentró *in vacuo* para producir compuesto (e) como un aceite marrón movedizo; ¹H nmr (d₆-DMSO, valores δ): 1.30 (6H, s); 3.90 (3H, s); 4.84 (1H, m); 7.76 (1H, m); 7.89 (1H, m); 8.16(1H, m).

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H

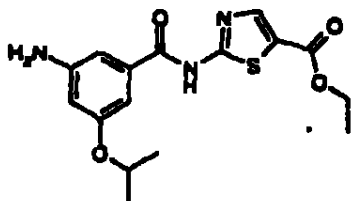
Compuesto (f)

2M Hidróxido de sodio (12.3ml, 24.7mM) se agregó a una solución ácido metil (3-nitro-5-isopropoxi) benzoico (1.18g, 4.9mM) en metanol (60ml) y se agitó durante 5 horas a temperatura ambiente. La mezcla de reacción se concentró entonces *in vacuo*, se acidificó a pH 1-2 con 2M ácido clorhídrico, el precipitado se filtró, se lavó con agua y se secó bajo alto vacío sobre gel de sílice. Compuesto (f) se obtuvo como un sólido blancuzco (1.04g, 94%); ^1H nmr (d_6 -DMSO, valores δ): 1.30 (6H, s); 4.81 (1H, m); 7.74 (1H, m); 7.85 (1H, m); 8.14 (1H, m). MS ($\text{M}-\text{H}^+$)⁻ 224.



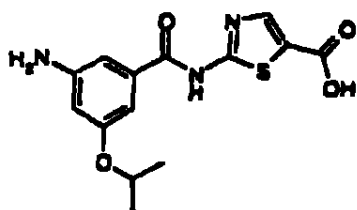
Compuesto (g)

Cloruro de oxalilo (0.75ml, 8.6mM) se agregó a ácido 3-nitro-5-isopropoxi benzoico (1.03g, 4.3mM) en diclorometano (50ml) que contenía dimetilformamida (2 gotas) bajo una atmósfera de argón a temperatura ambiente. Después de 3 horas la mezcla de reacción se concentró *in vacuo* y se sometió a destilación bajo temperatura fija con tolueno para producir un aceite anaranjado el cual se disolvió en diclorometano (40ml). Se agregaron 2-aminotiazol-5-carboxilato de etilo (0.89g, 5.1mM), diisopropiletilamina (1.77g, 10.3mM) y N,N-dimetilaminopiridina (50mg, 0.43mM) y se agitaron durante 1 hora bajo una atmósfera de argón. Después de esto la mezcla de reacción se concentró *in vacuo*, luego el residuo marrón pálido se purificó en gel de sílice usando 15 a 20% acetato de etilo/isohexano como eluyente. Compuesto (g) se obtuvo como un sólido amarillo pálido (1.56g, 92%); ^1H nmr (d_6 -DMSO, valores δ): 1.32 (6H, d); 4.88 (1H, m); 7.87 (1H, s); 8.05 (1H, s); 8.14 (1H, s); 8.45 (1H, s).



Compuesto (h)

Se agregó 10% paladio sobre carbono (20mg) bajo una atmósfera de argón a una solución de 2-[(3-isopropoxi-5-nitro)benzoilamino]-5-tiazolcarboxilato de etilo (209mg, 0.53mM) en acetato de etilo (35ml). Se introdujo gas de hidrógeno y la mezcla de reacción se agitó vigorosamente durante 18 horas antes de filtrar a través de celita y la concentración *in vacuo* para producir compuesto (h) como un sólido amarillo pálido (160mg, 83%); ¹H nmr (d6-DMSO, valores δ): 1.25 (6H, d); 1.29 (3H, t); 4.28 (2H, q); 4.58 (1H, m); 5.31 (2H, br s); 6.33 (1H, m); 6.81 (1H, m); 6.87 (1H, s); 8.17 (1H, s).

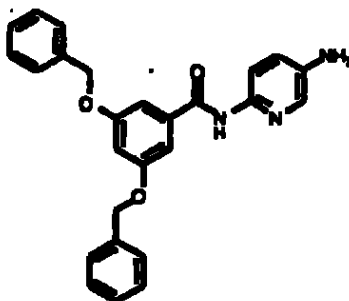


Compuesto (k)

2M Hidróxido de sodio (0.3ml, 0.57mM) se agregó a una solución 2-[(3-isopropoxi-5-amino)benzoilamino]-5-tiazolcarboxilato de etilo (40mg, 0.11mM) en tetrahidrofurano (1.2ml) / metanol (0.5ml) y se calentó a 50°C durante 5 horas, luego a temperatura ambiente durante la noche. La mezcla de reacción se concentró luego *in vacuo*, se acidificó a pH 4-5 con 2M ácido clorhídrico, el precipitado se filtró, se lavó con agua y se secó bajo alto vacío sobre sílice. Compuesto (k) se obtuvo como un sólido rojizo-marrón (35mg, 100%); ¹H nmr (d6 DMSO, valores δ): 1.27 (6H, d); 4.63 (1H, m); 6.58 (1H, s); 7.05 (1H, s); 7.16 (1H, s); 8.14 (1H, s).

EJEMPLO H

Ruta 7: 2-[(3,5-dibenciloxibenzoil)amino]-5-aminopiridina

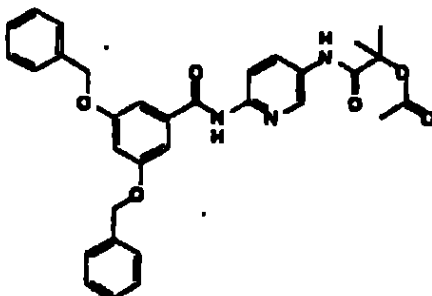


A una solución agitada de 2-[(3,5-dibenciloxibenzoil)amino]-5-nitropiridina (910 mg) en DMF (6 ml) se agregó polvo de zinc (1300 mg) y una solución hexahidrato de cloruro férrico (1700 mg) en agua (6 ml). La mezcla resultante se agitó a 120°C durante tres horas. Se dejó enfriar a temperatura ambiente. La mezcla se extrajo con acetato de etilo. El extracto se lavó con agua (50 ml), salmuera (50 ml), se secó sobre MgSO₄, luego se retiró el material volátil por evaporación para dejar un sólido, el cual se secó bajo alto vacío durante 24 horas a 100°C para producir el compuesto del título (518 mg) como un sólido, ¹H NMR δ (d₆-DMSO): 5.17 (m, 6H), 6.80 (s, 1H), 7.00 (d, 1H), 7.26 a 7.46 (m, 12H), 7.71 (s, 1H), 7.78 (d, 1H), 10.28 (br s, 1H). MS ES⁺ 426.52 (M+H)⁺.

El material inicial 6-[(3,5-dibenciloxibenzoil)amino]-3-nitropiridina requerida se preparó por un método análogo al dado en Ejemplo A (ruta 1), a partir de 2-amino-5-nitropiridina; ¹H NMR δ (d₆-DMSO): 5.18 (s, 4H), 6.90 (s, 1H), 7.29-7.50 (m, 12H), 8.42 (d, 1H), 8.64 (d, 1H), 9.23 (s, 1H), 11.46 (br s, 1H). MS ES⁺ 456.12 (M+H)⁺.

EJEMPLO I

Ruta 8: N-{6-[3,5-dibenciloxibenzoil)amino]-piridin-3-il}-2-acetoxi-2-metil-propionamida

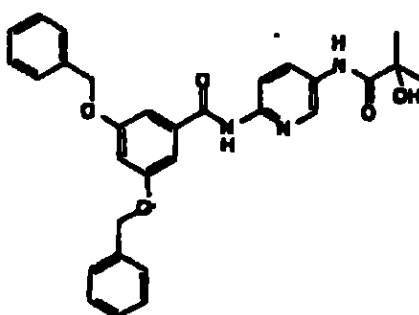


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A una solución agitada de 2-[(3,5-dibenciloxibenzoil)amino]-5-aminopiridina (200 mg) en THF (2 ml) y piridina (2 ml) se agregó una solución de cloruro de 2-acetoxiisobutirilo (98 mg) en THF (1 ml). La mezcla se agitó a temperatura ambiente durante 16 horas. El material volátil se retiró por evaporación. El residuo se disolvió en acetato de etilo (50 ml), se lavó con agua (25 ml), salmuera (25 ml), se secó sobre MgSO₄. El material volátil se retiró por evaporación para dejar una goma que se trituró bajo éter para producir el compuesto del título (211 mg) como un sólido, ¹H NMR δ (d₆-DMSO): 1.55 (s, 6H), 2.08 (s, 3H), 5.18 (s, 4H), 6.85 (s, 1H), 7.29.to 7.50 (m, 12H), 7.98 (dd, 1H), 8.13 (d, 1H), 8.61 (s, 1H), 9.70 (s, 1H), 10.72 (s, 1H) MS ES⁻ 552.22 (M-H)⁻.

EJEMPLO J

Ruta 9: N-{6-[(3,5-dibenciloxibenzoil)amino]-piridin-3-il}-2-hidroxi-2-metil-propionamida

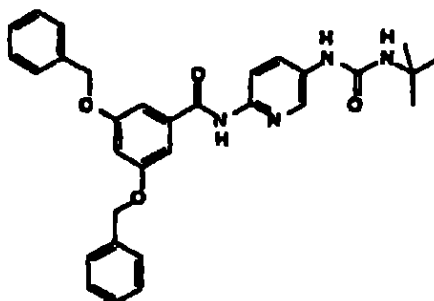


A una suspensión agitada de N-{6-[(3,5-dibenciloxibenzoil)amino]-piridin-3-il}-2-acetoxi-2-metil-propionamida (158 mg) en metanol (10 ml) se agregó una solución de LiOH.H₂O (30 mg) en agua (1 ml) y THF (3 ml). La mezcla se agitó a temperatura ambiente durante 20 horas. El material volátil se retiró por evaporación. Al residuo se agregó agua (10 ml). Se acidificó con 2M ácido clorhídrico. El precipitado se extrajo por filtración, se lavó con acetato de etilo, y se secó bajo alto vacío para producir el compuesto del título (120 mg) como un sólido, ¹H NMR δ (d₆-DMSO): 1.35 (s, 6H), 5.18 (s, 4H), 6.88 (s, 1H), 7.28 a 7.48 (m, 12H), 8.08 (d, 1H), 8.22 (d, 1H), 8.82 (s, 1H), 9.90 (s, 1H), 10.96 (s, 1H). MS ES⁺ 512.16 (M+H)⁺.

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EJEMPLO K

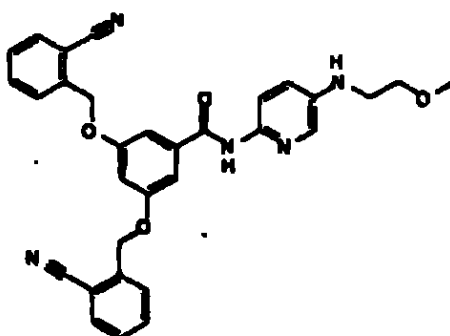
Ruta 10: 3,5-dibenciloxi-N-(5-[(*tert*-butilamino)carbonil]amino} piridin-2-il)benzamida



Una solución de *tert*-butil isocianato (51 mg) en THF (5 ml) se trató con 2-[(3,5-dibenciloxibenzoil)amino]-5-aminopiridina (212 mg), y se agitó a temperatura ambiente durante 24 horas. Se agregó más *tert*-butil isocianato (0.34 ml), y la agitación se continuó a temperatura ambiente durante 4 días más. El material volátil se retiró por evaporación y el residuo se trituró bajo metanol para producir el compuesto del título (159 mg) como un sólido, ¹H NMR δ (d₆-DMSO): 1.30 (s, 9H), 5.18 (s, 4H), 6.09 (s, 1H), 6.85 (s, 1H), 7.32 a 7.50 (m, 12H), 7.78 (dd, 1H), 8.04 (d, 1H), 8.38 (s, 1H), 8.44 (s, 1H), 10.65 (s, 1H). MS ES⁺ 525.61 (M+H)⁺.

EJEMPLO L

Ruta 11: 3,5-di(2-cianobenciloxi)-N-{5-[2-metoxietil]amino} piridin-2-il}benzamida



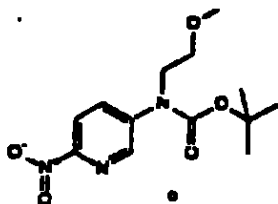
A una solución agitada de *tert*-butil 6-({3,5-di(2-cianobenciloxi)benzoil} amino)piridin-3-il(2-metoxietil)carbamato (237 mg) en diclorometano (10 ml) se agregó ácido trifluoroacético (3 ml). La solución se agitó a temperatura ambiente durante tres horas. El material volátil se retiró por

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evaporación. El residuo se diluyó en DCM (100 ml), se lavó con 2M hidróxido de sodio (50 ml), salmuera (50 ml), se secó sobre MgSO_4 . El material volátil se retiró por evaporación para producir el compuesto del título (190 mg) como una espuma, ^1H NMR δ (d_6 -DMSO): 3.22 (t, 2H), 3.28 (2, 3H), 3.50 (t, 2H), 5.31 (s, 4H), 6.92 (s, 1H), 7.12 (dd, 1H), 7.34 (s, 2H), 7.57 (m, 2H), 7.75 (m, 5H), 7.82 (d, 1H), 7.91 (d, 2H), 10.49 (br s, 1H). MS ES^+ 534.41 ($\text{M}+\text{H}$) $^+$.

Los materiales iniciales requeridos se prepararon como sigue:

Preparación de *tert*-butil 2-nitropiridin-5-il(2-metoxietil)carbamato

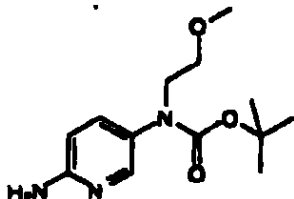


A una suspensión de Cs_2CO_3 (1430 mg) en tolueno se agregó 2-nitro-5-bromopiridina (406 mg), $\text{Pd}(\text{Ac})_2$ (44 mg), 1,1-bis(difenilfosfina)ferroceno (322 mg) y 2-metiloxietil amina (0.26 ml). La mezcla se agitó a 85°C , bajo nitrógeno, durante 16 horas. Se dejó enfriar a temperatura ambiente. Se diluyó con acetato de etilo (100 ml), y se filtró a través de un tapón de celita. El material volátil se retiró por evaporación, el residuo se purificó por cromatografía de destello en sílice, se eluyó con 50-100% acetato de etilo en hexano para producir un sólido que se agregó a una solución de di-*tert*-butil-dicarbonato (436mg) y N-dimetil-aminopiridina (cat) en THF (10 ml). La solución se agitó durante 14 horas a 75°C . Se dejó enfriar a temperatura ambiente, luego el material volátil se retiró por evaporación. El residuo se disolvió en acetato de etilo (100 ml), se lavó con agua (50 ml), salmuera (50 ml), se secó sobre MgSO_4 . El material volátil se retiró por evaporación, el residuo se purificó por cromatografía de destello en sílice, se eluyó con 20-40% acetato de etilo en hexano para producir el compuesto del título (359 mg) como una goma, ^1H NMR δ (CDCl_3): 1.49 (s, 9H), 3.33

(s, 6H), 3.62 (t, 2H), 3.86 (t, 2H), 8.06 (dd, 1H), 8.21 (d, 1H), 8.65 (s, 1H).
MS ES⁺ 298.35 (M+H)⁺.

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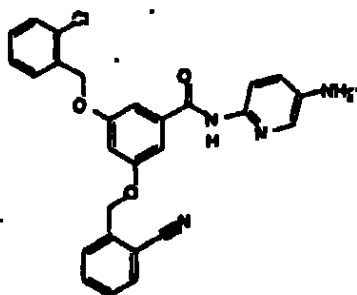
Preparación de *tert*-butil 2-aminopiridin-5-il(2-metoxietil)carbamato



A una solución de *tert*-butil 2-(6-nitropiridin-3-il)-4-metoxibutanoato (350 mg) en etanol (20 ml) y acetato de etilo (20 ml) se agregó 10 % paladio sobre carbono (100 mg). La suspensión se agitó a temperatura ambiente durante 16 horas bajo hidrógeno. Se filtró a través de celita, luego se recuperó el material volátil por evaporación para producir el compuesto del título (299 mg) como un sólido, ¹H NMR δ (d₆-DMSO): 1.32 (br s, 9H), 3.18 (s, 3H), 3.34 (t, 2H), 3.56 (t, 2H), 5.8 (s, 2H), 6.37(d, 1H), 7.17 (dd, 1H), 7.70 (d, 1H). MS ES⁺ 268.34 (M+H)⁺.

EJEMPLO M

Ruta 12: *N*-(5-aminopiridin-2-il)-3-[(2-clorobencil)oxi]-5-[(2-cianobencil)oxi]benzamida

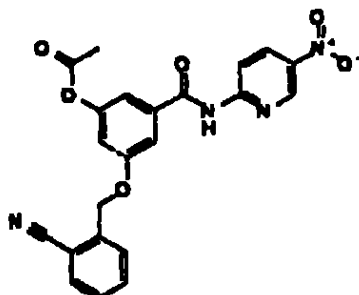


El compuesto del título se preparó de *N*-(5-nitropiridin-2-il)-3-[(2-clorobencil)oxi]-5-[(2-cianobencil)oxi]benzamida usando un método similar al descrito en Ruta 7.

Los materiales iniciales requeridos se prepararon como sigue:

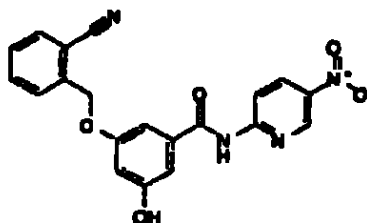
760,39

Preparación de 3-[[[(5-nitropiridin-2-il)amino]carbonil]-5-[(2-cianobencil)oxi]fenil acetato



A una solución agitada de ácido 3-acetoxi, 5-(2-cianobenciloxi)benzoico (8760 mg) en THF (100 ml) se agregó cloruro de oxalilo (3.6 ml) y DMF (0.5 ml). La mezcla se agitó a temperatura ambiente durante 3 horas. El material volátil se retiró por evaporación. El residuo se disolvió en una mezcla de THF (60 ml) y piridina (40 ml). Se agregó 2-amino-5-nitropiridina (3919 mg). La mezcla agitada se calentó a 55°C durante 16 horas. El material volátil se retiró por evaporación para dejar una goma que se purificó por cromatografía de destello en sílice, se eluyó con 1-5% acetato de etilo en hexano para producir el compuesto del título (6200 mg) como un sólido, ^1H NMR δ (d_6 -DMSO): 2.29 (s, 3H), 5.37 (s, 2H), 7.17 (s, 1H), 7.45 (s, 1H), 7.58 (m, 1H), 7.70 (s, 1H), 7.76 (m, 2H), 7.92 (d, 1H), 8.40 (d, 1H), 8.65 (dm, 1H), 9.21 (m, 1H), 11.57 (s, 1H). MS ES^+ 433.48 ($\text{M}+\text{H}$) $^+$.

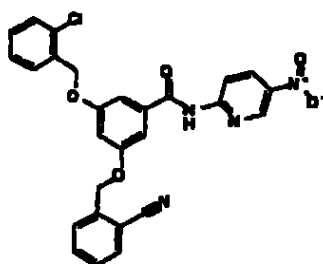
Preparación de N-(5-nitropiridin-2-il)-3-[(2-cianobencil)oxi]-5-hidroxibenzamida



Una suspensión de 3-[[[(5-nitropiridin-2-il)amino]carbonil]-5-[(2-cianobencil)oxi]fenil acetato (5710 mg) en THF (35 ml) se trató con 25% NaOMe en metanol (6 ml). Se agitó a temperatura ambiente durante 30

minutos. Se acidificó con 2M ácido clorhídrico (25 ml), luego se extrajo con acetato de etilo (100 ml). El extracto se lavó con agua (50 ml), salmuera 50 ml), se secó sobre MgSO₄. El material volátil se retiró por evaporación para producir un sólido. Éste se lavó con metanol caliente para producir el compuesto del título (4358 mg) como un sólido, LCMS rt = 2.38 min (90.5%). ES⁺ 391.45 (M+H)⁺.

Preparación de N-(5-nitropiridin-2-il)-3-[(2-clorohenzil)oxi]-5-[(2-cianobencil)oxi]benzamida

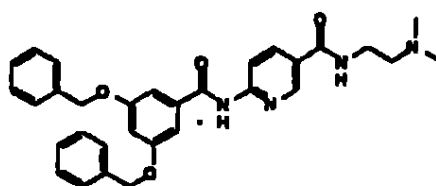


Una solución de N-(5-nitropiridin-2-il)-3-[(2-cianobencil)oxi]-5-hidroxibenzamida (195 mg) en DMF (3 ml) se trató con Ag₂CO₃ (165 mg) y 2-clorobencil bromuro (0.073 ml). Se calentó a 85°C y se agitó durante 17 horas bajo nitrógeno. Se dejó enfriar a temperatura ambiente. Se agregó (25 ml). Se extrajo con acetato de etilo (50 ml), se lavó con salmuera (25 ml), se secó sobre MgSO₄. El material volátil se retiró por evaporación para producir un sólido, el cual se purificó por cromatografía de destello en sílice, se eluyó con 0-5% acetato de etilo en diclorometano para producir el compuesto del título (43 mg) como un sólido, ¹H NMR δ (d₆-DMSO): 5.20 (s, 2H), 5.33 (s, 2H), 6.96 (s, 1H), 7.40 (m, 5H), 7.57 (m, 2H), 7.72 (m, 2H), 7.90 (d, 1H), 8.40 (d, 1H), 8.64 (dd, 1H), 9.22 (s, 1H), 11.50 (s, 1H). LCMS rt = 3.27 min (97.4%), ES⁺ 515.50 (M+H)⁺

EJEMPLO N

Ruta 13: 6-[[3,5-Di-(benciloxi)benzoil]amino]-N-[2-(dimetilamino)etil]nicotinamida

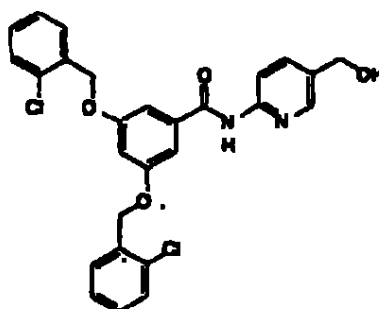
76,51



Diisopropiletilamina (DIPEA, 0.23ml, 1.3mM), luego 1-(3-dimetilaminopropil)-3-etil-carbodiimida (EDC, 126mg, 0.66mM) se agregaron a una solución de 2-dimetilaminoetilamina (0.57ml, 0.53mM) y ácido 6-[[3,5-di-(benciloxi)benzoil]amino]nicotínico (0.20g, 0.44mM) en diclorometano 10ml) bajo argón a temperatura ambiente. Después de 16 horas la mezcla de reacción se evaporó *in vacuo* y luego se cromatografió en SiO₂ usando una elusión de gradiente de 10 a 25% metanol en diclorometano. Las fracciones que contenían el producto se evaporaron para producir un sólido color crema (0.052g, 25%); ¹H NMR δ (d₆-DMSO): 2.67 (6H, s); 3.11 (2H, m); 3.62 (2H, m); 5.18 (4H, s); 6.88 (1H, s); 7.27-7.52 (12H, br m); 8.18-8.36 (2H, m); 8.90 (1H, s); 10.20 (1H, br s).

EJEMPLO O

Ruta 14: 2-[3,5-Di-(2-clorobenciloxi) benzoilamino]-5-hidroximetil piridina



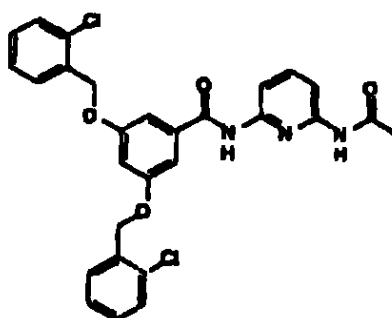
A una solución fría (-15 °C) de ácido 2-[3,5-di-(2-clorobenciloxi)benzoil]amino]-piridin-5-carboxílico (305 mg, 0.59 mmol) en dimetoxi etano (5ml) se agregó 4-metil)morfolina (80μl, 1eq) e isobutil cloroformato (76μl, 1.02 eq). La mezcla de reacción se agitó a -15 °C durante 15 minutos y luego se filtró; el residuo se lavó con dimetoxi etano

1623

(5x1ml). El filtrado y los lavados se enfriaron a -15 °C y se trataron con una suspensión de borohidruro de sodio (22mg, 1eq) en agua (1ml). Una vez cesada la efervescencia, se agregó agua (50ml) y acetato de etilo (30ml); la mezcla de reacción se evaporó a sequedad y el residuo se absorbió en sílice. El compuesto requerido se aisló por cromatografía de destello (eluyendo con 5% metanol en diclorometano) para producir el compuesto del título como un sólido incoloro (97 mg), ¹H NMR δ (d₆-DMSO): 4.5 (1H, d), 5.25 (s, 4H), 6.9 (s, 1H), 7.40 (m, 6H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (dd, 1H), 8.10 (d, 1H), 8.3 (s, 1H), 10.8 (br s, 1H); LCMS rt = 3.25 min (100%), ES⁺ 509 (M+H)⁺.

EJEMPLO P

Ruta 15: N-{6-[3,5-di-(2-clorobenciloxibencil)amino]-piridin-2-il}-2-acetamida



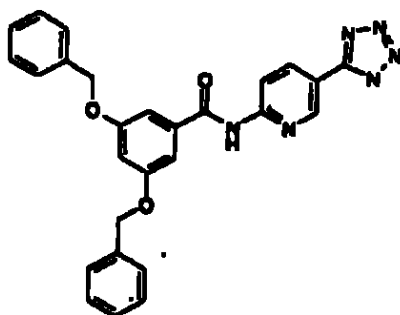
A una solución de 2-[(3,5-di-(2-clorobenciloxibenzoil)amino]-6-aminopiridina (220 mg, 0.45 mmol) en tetrahydrofurano (4 ml) se agregó piridina (43 mg, 0.54 mmol) y cloruro de acetilo (42 mg, 0.54 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con éter dietílico y se lavó sucesivamente con agua, 1M ácido cítrico, y agua; la solución se secó sobre sulfato de magnesio y el solvente se retiró *in vacuo* para producir un sólido amarillo (154mg). La trituración con metanol produjo el compuesto del título (75mg), ¹H NMR δ (4-DMSO): 3.3 (3H, s), 5.25 (s, 4H), 6.95 (s, 1H), 7.3 (d, 2H), 7.4 (m, 4H), 7.5 (m, 2H), 7.6 (m, 2H), 7.7 (m, 1H), 7.8 (m, 2H), 10.14 (br s, 1H), 10.36 (br s, 1H); ES⁺ 536/538 (M+H)⁺.

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El material inicial, 2-[(3,5-di-(2-clorobenciloxibenzoil)amino]-6-aminopiridina, se ejemplifica aquí como Ejemplo número 106.

EJEMPLO Q

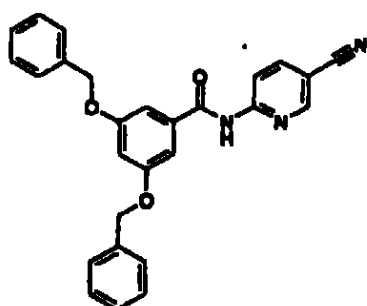
Ruta 16: 3,5-bis(benciloxi)-N-[5-(1H-tetrazol-5-il)piridin-2-il]benzamida



Azida de tributiltina (156 μ L, 0.57 mmol) se agregó a una suspensión de 3,5-bis(benciloxi)-N-(5-cianopiridin-2-il)benzamida (180 mg, 0.41 mmol) en tolueno (3 mL). La mezcla se calentó a reflujo durante 16 horas. La suspensión se enfrió y dividió en porciones entre acetato de etilo y ácido clorhídrico (1M). La capa orgánica se concentró *in vacuo* y el residuo se purificó por MPLC en sílice (eluyendo con 1% metanol / DCM a 15% metanol / DCM). El tetrazol se obtuvo como un sólido incoloro (113 mg, 57%). ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 6.88 (1H, s); 7.26-7.48 (12H, m); 8.40 (1H, d); 8.46 (1H, dd); 9.04 (1H, s); 11,13 (1H, br s); m/z (LCMS; ESI+) 479 (MH^+).

El material inicial requerido se preparó como sigue:

Preparación de 3,5-bis(benciloxi)-N-(5-cianopiridin-2-il)benzamida



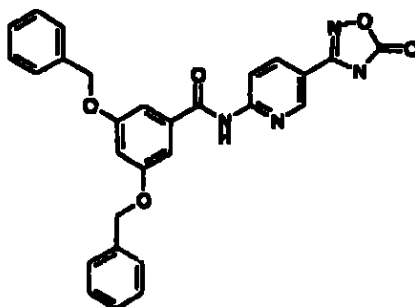
164
76

El compuesto del título se preparó como se describe en Ejemplo A (ruta 1), a partir de 2-amino-5-cianopiridina y 3,5-bis(benciloxi) benzoil cloruro, ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 6.89 (1H, m); 7.26-7.46 (12H, m); 8.27 (1H, dd), 8.33 (1H, d); 8.84 (1H, s); 11.23 (1H, br s); m/z (LCMS; ESI+) 436 (MH^+).

El material inicial 2-amino-5-cianopiridina requerida puede obtenerse (Bionet Research, y otros porveedores), o puede prepararse de acuerdo con el método dado en WO95/06034.

EJEMPLO R

Ruta 17; 3,5-bis(benciloxi)-N-[5-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)piridin-2-il]benzamida

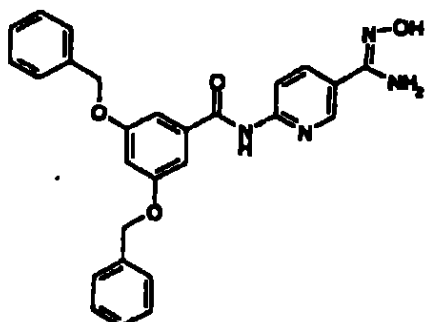


Cloroformate de etilo (32 μL , 0.33 mmol) se agregó a una solución de 3,5-bis (benciloxi)-N-(5-[(hidroxiamino)(imino)metil]piridin-2-il}benzamida (140 mg, 0.30 mmol) en piridina (5 mL). Esta solución se calentó a reflujo durante la noche. La mezcla se enfrió y se concentró bajo presión reducida. Se utilizaron DCM y metanol para disolver el material remanente y la solución se lavó con agua. La solución orgánica se concentró bajo presión reducida y el residuo se purificó en sílice por MPLC (fluyendo primeramente con 5% metanol / DCM luego 10% metanol / DCM). El compuesto del título se obtuvo como un sólido incoloro (103 mg, 70%). ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 6.87 (1H, s); 7.28-7.46 (12H, m); 8.21 (1H, dd); 8.38 (1H, d); 8.79 (1H, s); 11.14 (1H, br s); m/z (LCMS; ESI+) 495 (MH^+).

766105

El material inicial requerido se preparó como sigue:

Preparación de 3,5-bis(benciloxi)-N-{5-[(hidroxiamino)(imino)metil]piridin-2-il}benzamida

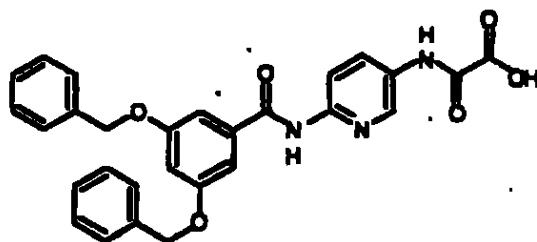


Una mezcla de 3,5-bis(benciloxi)-N-(5-cianopiridin-2-il)benzamida (212 mg, 0.49 mmol), trietilamina (170 μ L, 1.22 mmol) e hidroxilamina clorhidrato (85 mg, 1.22 mmol) en etanol (5 mL) se calentó a reflujo durante la noche. La mezcla se enfrió y se concentró bajo presión reducida. El residuo se purificó por MPLC en sílice eluyendo con 5% metanol / DCM luego 15% metanol / DCM. El compuesto del título se obtuvo como un sólido incoloro (171 mg, 75%). ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 5.92 (2H, s), 6.87 (1H, s); 7.28-7.48 (12H, m); 8.06 (1H, dd); 8.17 (1H, d), 8.65 (1H, s); 9.68 (1H, s); 10.85 (1H, br s); m/z (LCMS; ESI+) 469 (MH^+).

La 3,5-bis(benciloxi)-N-(5-cianopiridin-2-il)benzamida requerida se preparó como se describe en Ejemplo P (ruta 15).

EJEMPLO S

Ruta 18: Ácido [(2-{[3,5-bis(benciloxi)benzoil]amino}piridin-5-il)amino] (oxo)acético



Cloruro de metil oxalilo (37 μ L, 0.4 mmol) se agregó a una mezcla de N-(5-aminopiridin-2-il)-3,5-bis(benciloxi)benzamida (150 mg, 0.36 mmol) y

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triethylamina en DCM (5 mL). La mezcla se agitó durante 1 hora bajo una atmósfera de nitrógeno. La solución se diluyó con DCM y se lavó con agua. Los orgánicos se concentraron bajo presión reducida y el residuo se purificó en sílice por MPLC (eluyendo con 1% metanol / DCM a 15% metanol / DCM) para producir un sólido incoloro (110 mg). Este material se disolvió en THF (2 mL). Se agregaron agua (3mL) e hidróxido de sodio (0.5 mL, 2M, 1 mmol). La mezcla se agitó durante 1 hora antes de acidificarse con ácido clorhídrico (2M) y se diluyó con agua. El precipitado resultante se aisló por filtración, se lavó con agua y se secó *in vacuo*. El compuesto del título se obtuvo como un sólido incoloro (88 mg, 50%). ¹H NMR δ (d₆-DMSO): 5.18 (4H, s); 6.88 (1H, s); 7.30-7.50 (12H, m); 8.17 (2H, s); 8.79 (1H, s); 10.79 (1H, s); 10.93 (1H, br s); ^{m/z} (LCMS; ESI+) 498 (MH⁺).

El material inicial requerido se preparó de acuerdo con Ejemplo H (ruta 7).

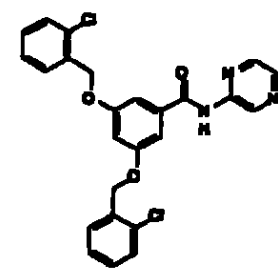
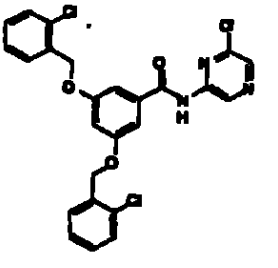
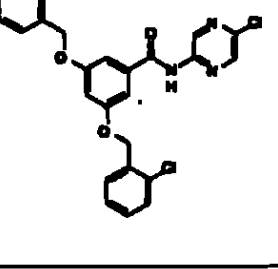
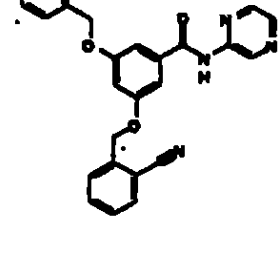
EJEMPLO T:

Por métodos análogos a los descritos más arriba se elaboraron además los siguientes compuestos, Ejemplos número T₁ a T₂₀.

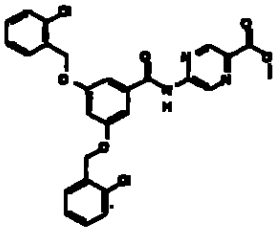
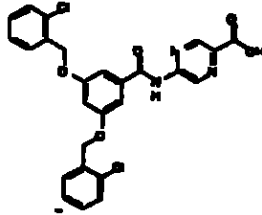
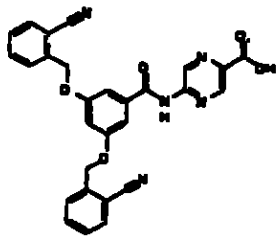
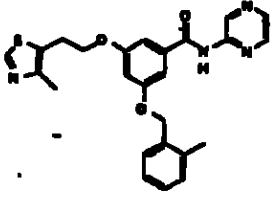
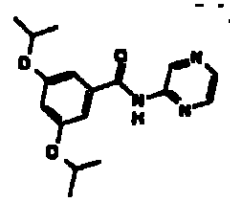
Compuesto T₉ se preparó por Ruta 1b (síntesis multi-paralela), como sigue. Al ácido apropiado (6.0 mmol) en diclorometano (25 mls) se agregó 1 gota de dimetilformamida y la mezcla se agitó a temperatura ambiente bajo argón, se agregó el cloruro de oxalilo (0.867 mls) al ácido y se agitó a temperatura ambiente durante 2 horas. El solvente se retiró en Genevac DD4, y el residuo resultante se sometió a destilación bajo temperatura fija con diclorometano (3 x 10 mls), luego se secó bajo alto vacío durante 2 horas. El cloruro de ácido resultante se disolvió entonces en THF (30 mls) y se agregó 5 mls de la solución a uno del conjunto de seis aminas en THF / Piridina (5mls). La mezcla resultante se agitó durante la noche a temperatura ambiente, se diluyó con acetato de etilo (5mls). La solución resultante se transfirió al extractor automatizado Allex y se lavó con agua

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(2x5mls), carbonato hidrogenado de sodio (5mls), 1M ácido cítrico (5mls), salmuera (5mls), se secó (sulfato de magnesio) y se evaporó en Genevac DD4. La goma resultante se trituró con metanol (1-2 mls) y el sólido resultante se filtró, se lavó con metanol y se secó con aire.

Ejemplo	Estructura	Ruta	NMR
1		1	¹ H NMR d (d6-DMSO): 5.26 (4H, s); 6.96 (1H, m); 7.38-7.45 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 8.43 (1H, d); 8.49 (1H, m); 9.42 (1H, m); 11.13 (1H, s).
2		1	¹ H NMR d (d6-DMSO): 5.25 (4H, s); 6.97 (1H, m); 7.38-7.45 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 8.64 (1H, d); 9.26 (1H, d); 11.33 (1H, s).
3		1	¹ H NMR d (d6-DMSO): 5.24 (4H, s); 6.95 (1H, s); 7.35-7.40 (6H, m); 7.50 (2H, m); 7.60 (2H, m); 8.61 (1H, s); 9.22 (1H, s); 11.25 (1H, br s).
4		1	¹ H NMR d (d6-DMSO): 5.36 (4H, s); 7.00 (1H, m); 7.44 (2H, d); 7.55-7.64 (2H, m); 7.77 (4H, m); 7.93 (2H, d); 8.43 (1H, d); 8.49 (1H, m); 9.43 (1H, s); 11.17 (1H, s).
5		1	¹ H NMR d (d6-DMSO): 3.90 (3H, s); 5.24 (4H, s); 6.97 (1H, m); 7.39 (6H, m); 7.50

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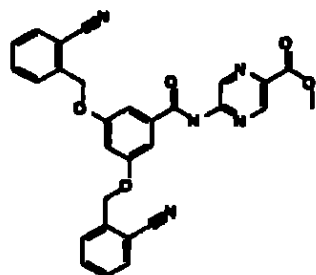
Ejemplo	Estructura	Ruta	NMR
			(2H, m); 7.60 (2H, m); 9.02 (1H, s); 9.52 (1H, s); 11.54 (1H, br s).
6		2	¹ H NMR d (d ₆ -DMSO): 5.24 (4H, s); 6.96 (1H, m); 7.39 (6H, m); 7.51 (2H, m); 7.62 (2H, m); 8.98 (1H, s); 9.48 (1H, s); 11.44 (1H, br s).
7		2*	¹ H NMR d (d ₆ -DMSO): 5.34 (4H, s); 7.00 (1H, s); 7.57 (2H, m); 7.75 (4H, m); 7.91 (2H, d); 9.00 (1H, s); 9.52 (1H, s); 11.53 (1H, s); 13.43, (1H br s).
8		1	¹ H NMR d (d ₆ -DMSO): 2.29 (3H, s); 2.33 (3H, s); 3.24 (m, 2H); 4.21 (2H, t); 5.12 (2H, s); 6.80 (1H, m); 7.21 (4H, m); 7.31 (1H, m); 7.40 (2H, m); 8.39 (1H, m); 8.45 (1H, m); 8.82 (1H, s); 9.38 (1H, s); 11.06 (1H, br s).
9		1b	¹ H NMR d (d ₆ -DMSO) 1.25 (d, 12H), 4.7 (hept, 2H) 6.6 (d, 1H), 7.2 (d, 2H), 8.4 (d, 1H), 8.45 (t, 1H), 9.4 (s, 1H), 11.0 (br s, 1H)
10		1	¹ H NMR δ (d ₆ -DMSO): 2.37 (s, 3H), 3.24 (t, 2H), 4.23 (t, 2H), 4.65 (d, 2H), 5.28

Ejemplo	Estructura	Ruta	NMR		
					(d, 1H), 5.42 (d, 1H), 6.05 (m, 1H), 6.75 (s, 1H), 7.23 (s, 2H), 8.43 (s, 1H), 8.84 (s, 1H), 9.40 (s, 1H), 11.07 (br s, 1H).
11		1			¹ H NMR δ (d ₆ -DMSO) 2.32 (s, 3H), 2.35 (s, 3H), 3.21 (t, 2H), 4.21 (t, 2H) 5.13 (s, 2H), 6.81 (s, 1H), 7.14-7.26 (m, 4H), 7.32 (1H, s), 7.41 (1H, d), 8.51 (s, 1H), 8.81 (s, 1H), 9.39 (s, 1H), 11.34 (brs. 1H)
12		1	364		¹ H NMR δ (d ₆ -DMSO): 2.12 (s, 6H), 3.81 (s, 3H), 5.05 (s, 2H), 6.95 (s, 1H), 7.05 (s, 2H), 7.1 (s, 1H), 7.72 (d, 1H), 7.78 (s, 1H), 8.36 (d, 1H), 8.43 (s, 1H), 9.4 (s, 1H), 10.92 (br s, 1H)
13		1b	412	410	
14		1b	330		
15		1b	288		

120
1/1
1

Ejemplo	Estructura	Ruta	NMR		
16		1b	312		
17		1b	452		
18		1b	400		
19		2a, 1c	428	426	δ_H (500MHz, DMSO- d_6) 1.28 (6H, d), 3.07 (2H, t), 4.26 (2H, t), 4.70 (1H, m), 6.71 (1H, m), 7.12 (1H, m), 7.24 (2H, m), 7.30 (1H, m), 7.46 (1H, m), 8.98 (1H, d), 9.48 (1H, d), 11.33 (1H, s), 13.24 (1H, br s)
20		1a	382		

* Por Ejemplo 7, el intermedio éster se preparó por ruta 1:



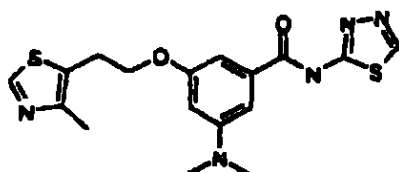
722191

^1H NMR δ (d_6 -DMSO): 3.90 (3H, s); 5.34 (4H, s); 7.01 (1H, s); 7.43 (2H, s); 7.58 (2H, m); 7.74 (4H, m); 7.91 (2H, d); 9.02 (1H, s); 9.52 (1H, s); 11.57 (1H, br s).

EJEMPLO U

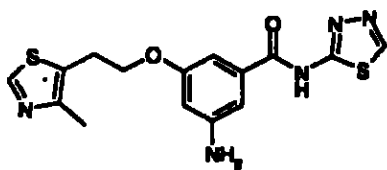
2-[3-{2-(4-Metil tiazol-5-il) etoxi}-5-dimetilamino] benzoilamino]-[1,3,4]-tiadiazol

(Ruta 19)

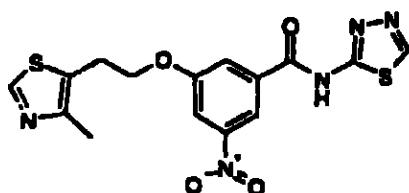


Formaldehído (37% en agua) (0.033ml, 0.44mM) se agregó a 2-[3-{2-(4-metil tiazol-5-il)etoxi}-5-amino]benzoilamino]-[1,3,4]-tiadiazol (27mg 0.074mM) y mallas moleculares 4A (0.2g) en metanol (4ml)/acetonitrilo (3ml)/ g.AcOH (2 gotas) bajo una atmósfera inerte a temperatura ambiente. Después de 150 minutos se agregó cianoborohidruro de sodio (7mg, 0.12mM) y la mezcla de reacción se agitó durante 40 horas. La mezcla de reacción se filtró, se concentró *in vacuo*, el residuo se acidificó con 2M HCl para precipitar un sólido incoloro. Purificado en gel de sílice (50 a 75% EtOAc/iso-hexano) produjo el compuesto del título como un sólido incoloro (25mg, 85%); ^1H NMR δ (d_6 -DMSO): 2.35 (s, 3H), 2.93 (s, 6H), 3.22 (m, 2H), 4.19 (m, 2H), 6.41 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 8.80 (s, 1H), 9.17 (s, 1H).

El material inicial requerido 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-amino] benzoilamino]-[1,3,4]-tiadiazol se preparó como sigue:

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F73

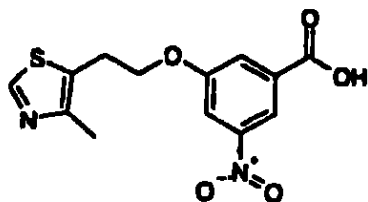
10% Paladio sobre carbono (80mg) se agregó bajo una atmósfera de argón a una solución de 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-nitro] benzoilamino]-[1,3,4]-tiadiazol (0.38g, 0.99 mM) en acetato de etilo (40ml). Se introdujo gas de hidrógeno y la mezcla de reacción se agitó vigorosamente durante 18 horas antes de filtrar a través de celita, la concentración *in vacuo* y sustitución del catalizador (80mg). Después agitar bajo gas de hidrógeno durante 18 horas más, se realizó un cambio final del catalizador. Después de lo cual la anilina cruda se purificó en gel de sílice (1 % a 4% MeOH/DCM) para producir 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-amino] benzoilamino]-[1,3,4]-tiadiazol como un sólido incoloro (0.1g, 28%); MS (M-H⁺) 360.



Cloruro de oxalilo (0.20ml, 2.35mM) se agregó a ácido 3-{2-(4-metil tiazol-5-il) etoxi}-5-nitro benzoico (0.72g, 2mM) en diclorometano (30ml) que contenía DMF (2 gotas) bajo una atmósfera de argón a temperatura ambiente. Después de 3 horas la mezcla de reacción se concentró *in vacuo* y se sometió a destilación bajo temperatura fija con tolueno para producir un sólido blancuzco. El cloruro de ácido y 2-amino [1,3,4]-tiadiazol (0.19g, 1.9 mM) se disolvieron en DCM (20ml), luego se agregaron DIPEA (0.96ml, 5.6 mM) y DMAP (0.04g, 0.3 mM). Después de agitar durante la noche bajo argón, la mezcla de reacción se concentró, se purificó en gel de sílice (50% a 75% a 100% EtOAc/iso-hexano) y produjo un sólido amarillo pálido que se trituró con MeOH para producir 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-nitro] benzoilamino]-[1,3,4]-tiadiazol como un sólido incoloro (0.30g, 48%); ¹H NMR δ (d₆-DMSO): 2.37 (s, 3H), 3.26 (t, 2H), 4.35 (t,

4/13
~~7/13~~

2H), 7.89 (m, 1H), 8.09 (s, 1H), 8.47 (s, 1H), 8.81 (s, 1H), 9.24 (s, 1H).

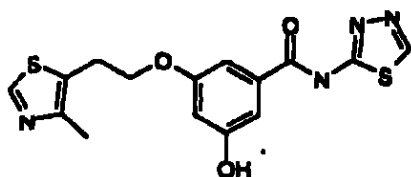


DIAD (3.16ml, 16.1 mM) se agregó a una solución agitada de 3-nitrohidroxil benzoato de metilo (2.11 g, 10.7mM), 4-(2-hidroxi etil)-5-metiltiazol (1.55ml, 12.8mM), y trifenilfosfina (4.21g, 16.1 mM) en THF (50ml) bajo una atmósfera de argón a temperatura ambiente. Después de 1 hora la mezcla de reacción se concentró *in vacuo*, el residuo se trituró con éter dietílico para producir un sólido incoloro (óxido de trifenilfosfina). Éter dietílico conc. para producir una goma marrón oscura, purificación en gel de sílice (50% a 75% EtOAc/iso-hexano) proporcionó el producto contaminado con DIAD reducida y óxido de trifenilfosfina (6.8g). El producto crudo se disolvió/suspendió en MeOH (80ml), se agregó 2M NaOH (20ml, 40 mM), se calentó a 65°C durante 4 horas, luego se enfrió y se concentró. El residuo se diluyó con agua (140ml)/ 2M NaOH (40ml), el óxido de trifenilfosfina precipitado se filtró, luego se acidificó con c. HCl a PH1-2. El precipitado se filtró, se lavó con agua, se secó bajo alto vacío para producir ácido 3-{2-(4-metil tiazol-5-il) etoxi}-5-nitro benzoico como un sólido incoloro (3.12g, 79% sobre 2 pasos): ¹H NMR δ (d₆-DMSO): 2.39 (s, 3H), 3.23 (t, 2H), 4.35 (t, 2H), 7.78 (s, 1H), 7.90 (m, 1H), 8.22 (s, 1H), 8.93 (s, 1H).

EJEMPLO V

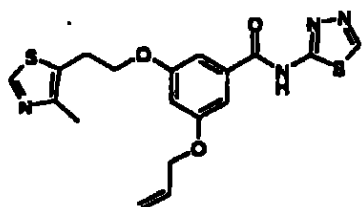
2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-hidroxi] benzoilamino]-[1,3,4]-tiadiazol

(Ruta 20)



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Una solución de 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-aliloxi] benzoilamino]-[1,3,4]-tiadiazol (1.1g, 2.7 mmol) en tetrahidrofurano (40ml) se agitó bajo una atmósfera de argón y se trató con ácido de Meldrum (0.79g, 5.4mmol) y tetrakis (trifenil fosfina) paladio (0) (825mg, 0.7mmol, 0.25 eq) y la solución amarilla resultante se agitó a temperatura ambiente durante 2 horas. Trituraciones secuenciales con diclorometano y tetrahidrofurano caliente arrojaron 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-hidroxi] benzoilamino]-[1,3,4]-tiadiazol como un sólido incoloro (0.59g, 59%), $^1\text{H NMR } \delta$ (d_6 -DMSO): 2.35 (s, 3H), 3.2 (t, 2H), 4.2 (t, 2H), 6.55 (m, 1H), 7.05 (s, 1H), 7.2 (s, 1H), 8.81 (s, 1H), 9.2 (s, 1H), 9.8 (br s, 1H); m/z 363 (M+H) $^+$, 361 (M-H) $^-$.

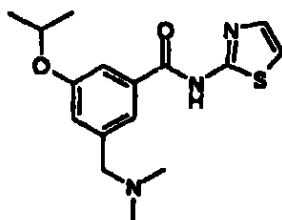


El material inicial 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-aliloxi] benzoilamino]-[1,3,4]-tiadiazol requerido se preparó de acuerdo con el método de alquilación genérico apropiado, y el ácido benzoico resultante se acopló con 1,3,4-tiadiazol de acuerdo con Ruta 1. Los datos analíticos de todos los intermedios fueron consistentes con las estructuras propuestas.

EJEMPLO W

2-(3-isopropoxi-5-dimetilaminometil)benzoil aminotiazol

(Ruta 21)



Una solución de 2-(3-isopropoxi-5-formil)benzoil aminotiazol (0.11g,

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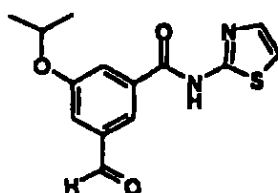
0.39mmol) en diclorometano se trató con dimetilamina (0.074ml de una solución de aprox. 5.6M en etanol, 0.41mmol, 1.1 eq) y se agitó bajo argón durante 10 minutos. A la solución se agregó tris-acetoxi borohidruro de sodio (0.11g, 0.53mmol, 1.4 eq), y la mezcla resultante se agitó durante la noche a temperatura ambiente. Seguidamente se agregaron otros reactivos (las mismas cantidades que antes) y la mezcla nuevamente se agitó durante la noche a temperatura ambiente. La solución se trató con solución de bicarbonato de sodio saturado (10ml) y se agitó durante 20 minutos; luego se extrajo dos veces con diclorometano, los extractos orgánicos se secaron sobre sulfato de magnesio y se evaporaron *in vacuo* para proporcionar el producto como un aceite incoloro. Éste se disolvió en acetato de etilo y la solución se trató con una solución eterificada de HCl (exceso de 1M); el precipitado así formado se filtró bajo argón y se lavó con éter dietílico para producir 2-(3-isopropoxi-5-dimetilaminometil)benzoil aminotiazol clorhidrato como un sólido incoloro (0.1g, 72%), ^1H NMR δ (d_6 -DMSO): 1.31 (d, 6H), 2.71 (s, 6H), 4.26 (m, 2H), 4.76 (m, 1H), 7.29 (d, 1H), 7.42 (m, 1H), 7.55 (d, 1H), 7.70 (s, 1H), 10.66 (bs, 1H).

El material inicial requerido se preparó como sigue:

EJEMPLO X

2-(3-isopropoxi-5-formil)benzoil aminotiazol

(Ruta 22):



Una solución de 2-(3-isopropoxi-5-hidroximetil)benzoil aminotiazol (0.115g, 0.39mmol) en tetrahidrofurano (8ml) se trató con dióxido de manganeso (0.27g, 3.1mmol, 8eq) y la suspensión resultante se agitó durante la noche a temperatura ambiente; se agregó oxidante adicional (0.1g

126
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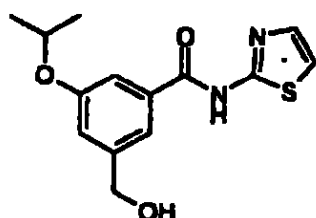
porciones) hasta que el material inicial se consumió (tlc). La suspensión se filtró, el residuo se lavó bien con acetato de etilo, y el filtrado combinado y los lavados se evaporaron *in vacuo* para proporcionar el producto como un sólido amarillo pálido, ^1H NMR δ (d_6 -DMSO): 1.31 (d, 6H), 4.82 (m, 1H), 7.26 (d, 1H), 7.56 (d, 1H), 7.59 (s, 1H), 7.94 (d, 1H), 8.15 (s, 1H), 10.00 (s, 1H), 12.77 (bs, 1H).

El material inicial requerido se preparó como sigue:

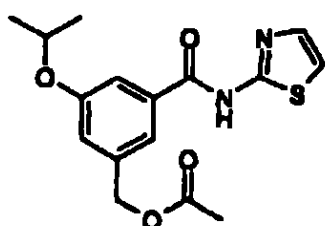
EJEMPLO Y

2-(3-isopropoxi-5-hidroximetil)benzoil aminotiazol

(Ruta 23)



La escisión del éster estándar de 2-(3-isopropoxi-5-acetoximetil)benzoil aminotiazol (0.15g, 0.46 mM) usando 2M NaOH/THF/MeOH durante 1 hora produjo 2-(3-isopropoxi-5-hidroximetil)benzoil aminotiazol como un sólido incoloro (0.149g, 100%); ^1H NMR δ (d_6 -DMSO): 1.28 (d, 6H), 4.51 (s, 2H), 4.71 (m, 1H), 7.05 (s, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 7.53 (d, 1H), 7.58 (s, 1H), 12.50 (bs, 1H).

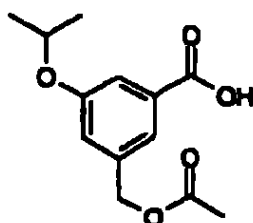


El 2-(3-isopropoxi-5-acetoximetil)benzoil aminotiazol requerido se preparó por un acoplamiento estándar entre 3-isopropoxi-5-acetoximetil benzoil cloruro y 2-aminotiazol de acuerdo con Ruta 1, para producir el compuesto

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del título como un aceite amarillo pálido, δ (d_6 -DMSO): 1.3 (d, 6H), 2.1 (s, 3H), 4.75 (hept, 1H), 5.1 (s, 2H), 7.15 (s, 1H), 7.25 (d, 1H), 7.65 (d, 1H), 7.6 (m, 2H), 12.6 (bs, 1H).

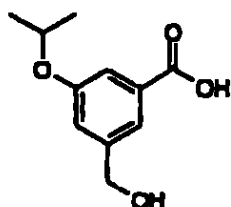
El ácido 3-isopropoxi-5-acetoximetil benzoico requerido se preparó como sigue:



Una solución de ácido 3-isopropoxi-5-hidroximetil benzoico (0.77g, 3.7mmol) en diclorometano (20ml) se enfrió (baño helado) y se agitó bajo argón; se agregó piridina (1.18ml, 14.6mmol, 4eq) seguida gota a gota por cloruro de acetilo (0.55ml, 7.7 mmol, 2.1 eq). La mezcla se agitó durante 5 minutos, luego se dejó calentar a temperatura ambiente durante 90 minutos. Se agregó agua (20ml), la mezcla se agitó durante 2 horas, luego se dejó reposar durante la noche. La capa orgánica se separó, la porción acuosa se lavó con diclorometano, y las fracciones de diclorometano se combinaron y se evaporaron. El aceite amarillo pálido resultante se disolvió en acetato de etilo y la solución se lavó con 0.05M CHI acuoso (20ml); la capa orgánica se separó, se secó sobre sulfato de magnesio y se evaporó *in vacuo* para proporcionar el producto como un sólido amarillo pálido, ^1H NMR δ (d_6 -DMSO): 1.25 (d, 6H), 2.06 (s, 3H), 4.65 (hept, 1H), 5.05 (s, 2H), 7.12 (s, 1H), 7.31 (d, 1H), 7.46 (s, 1H).

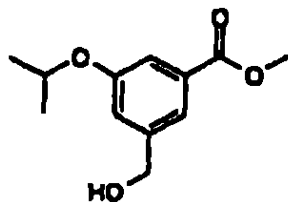
El material inicial ácido 3-isopropoxi-5-hidroximetil benzoico requerido se preparó como sigue:

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La escisión estándar 2M NaOH/THF/MeOH de metil 3-isopropoxi-5-hidroximetil benzoato (1.12g, 5.0 mM) produjo el compuesto del título como un sólido incoloro (0.98g, 94%); ^1H NMR δ (d_6 -DMSO): 1.25 (d, 6H), 4.47 (s, 2H), 4.60 (m, 1H), 5.23 (bs, 1H), 7.06 (s, 1H), 7.24 (s, 1H), 7.45 (s, 1H).

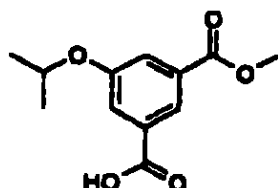
El material inicial requerido metil 3-isopropoxi-5-hidroximetil benzoato se preparó como sigue:



Mono-metil-5-isopropoxi-isoftalato (5.15g, 21.6 mM) se disolvió en THF (180ml), se enfrió a 2°C y complejo borano: THF (72ml de solución 1.5M en THF, 0.11 mM) se agregó gota a gota durante 15 minutos, manteniendo una temperatura interna de $<5^\circ\text{C}$. Después de 15 minutos la mezcla de reacción se calentó a temperatura ambiente, se agitó durante 3 horas antes de enfriar (baño helado) y extinguiendo con pedazos de hielo. Cuando ya no se observó ninguna reacción más, se agregó salmuera (150ml) / éter dietílico (150ml). La capa orgánica se retiró, se extrajo la acuosa con éter dietílico adicional (1 x 100ml), los orgánicos combinados se lavaron con salmuera (1 x 100ml), se secaron (MgSO_4), se filtraron y se concentraron. Se purificó en gel de sílice (20-25% EtOAc/isohehexano) para producir el compuesto del título como un sólido incoloro (3.57g, 74%); ^1H NMR δ (d_6 -DMSO): 1.26 (d, 6H), 3.82 (s, 3H), 4.50 (d, 2H), 4.63 (m, 1H), 5.26 (t, 1H (-OH)), 7.10 (s, 1H), 7.25 (s, 1H), 7.47 (s, 1H).

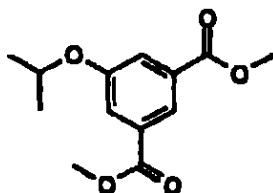
14279/66/1

El material inicial requerido mono-metil-5-isopropoxi-isoftalato se preparó como sigue:



2M NaOH (1.03g, 25.9 mM) en metanol (9 ml) se agregó a una solución de dimetil-5-isopropoxi-isoftalato (5.68g, 22.5 mM) en acetona (45ml) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró, se acidificó (2M HCl) a pH1-2, se filtró, se lavó con agua y se secó bajo alto vacío para producir 14279/66/1 como un sólido incoloro (5.25g, 98%) (contiene 15-20% diácido); MS (M-H⁺)⁻ 237.

El material inicial requerido dimetil-5-isopropoxi-isoftalato se preparó como sigue:

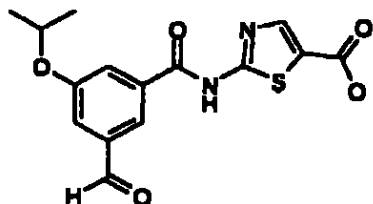


Dimetil-5-hidroxi-isoftalato (5.2g, 24.6 mM), carbonato de potasio (4.07g, 29.5 mM), yoduro de potasio (0.82g, 4.9 mM) y 2-bromopropano (2.4ml, 25.8 mM) en DMF (50ml) se calentó a 90°C durante 3 horas, después de lo cual se agregó 2-bromopropano adicional (2.4ml), carbonato de potasio (2.2g) se agregó, se calentó durante 4 horas más, luego se enfrió a temperatura ambiente y se concentró. Se agregó EtOAc (150ml), luego se lavó con agua, salmuera, se secó (MgSO₄), se filtró y se concentró para producir un aceite amarillo pálido que se solidificó al reposar (6.0g, 97%); MS (MH⁺) 253.

EJEMPLO Z

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Ácido 2-(3-isopropoxi-5-formil)benzoil aminotiazol-5-carboxílico (Ruta 24)

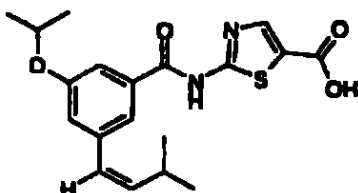


Una solución de ácido 2-(3-isopropoxi-5-hidroximetil)benzoil aminotiazol-5-carboxílico (0.42g, 1.25mmol) en tetrahidrofurano (50ml) se trató con periodinano Dess-Martin (DMP, 0.58g, 1.37mmol, 1.1 eq) y se agitó a temperatura ambiente durante 90 minutos. El solvente se retiró *in vacuo*, y el residuo se trató con diclorometano y se filtró. El residuo se dividió en porciones entre acetato de etilo y solución de bicarbonato de sodio saturado que contenía solución de tiosulfato de sodio (ca 7 eq de 2.1 M), y la mezcla 2-fases resultante se agitó vigorosamente antes de acidificarse a ca pH6. El compuesto del título se aisló por filtración como un sólido incoloro, (0.145g, 35%), ^1H NMR δ (d_6 -DMSO): 1.32 (d, 6H), 4.79 (m, 1H), 7.62 (m, 1H), 7.92 (m, 1H), 8.13 (s, 1H), 8.18 (s, 1H), 10.03 (s, 1H).

El material inicial requerido ácido 2-(3-isopropoxi-5-hidroximetil)benzoil aminotiazol-5-carboxílico se preparó de acuerdo con el procedimiento dado en Ruta 2a y se ejemplifica como Ejemplo II₈₁.

EJEMPLO AA

Z-{2-[3-isopropoxi-5-(3-metil-but-1-enil)]benzoil aminotiazol-5-carboxílico ácido}
(Ruta 25)



182281

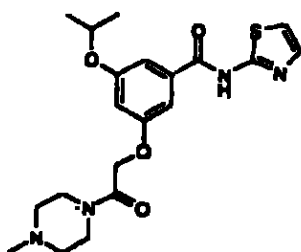
Una solución de bromuro de iso-butil trifenil fosfonio (0.45g, 1.13mmol, 3.1 eq) en tetrahidrofurano (20ml) se trató con t-butóxido de potasio (1.1ml de 1M en tetrahidrofuran, 1.13mmol, 3.1 eq) y se agitó a 0 °C bajo argón. A éste se agregó ácido 2-(3-isopropoxi-5-formil)benzoil aminotiazol-5-carboxílico (0.122g, 0.36mmol), y la solución resultante se agitó durante 100 minutos, dejando calentar a temperatura ambiente. Se agregó agua y el solvente se retiró *in vacuo*; el residuo se dividió en porciones entre agua y acetato de etilo y las capas se separaron. La porción acuosa se neutralizó (2M HCl) y se extrajo dos veces con acetato de etilo; los extractos orgánicos se secaron (MgSO₄), se filtraron y se concentraron y el residuo se purificó por cromatografía en gel de sílice (cartucho Bondelut 10g, eluyendo con diclorometano que contenía metanol, 10% v/v) para producir el compuesto del título como un sólido incoloro (0.012g, 9%); ¹H NMR δ (d₆-DMSO): 1.01 (d, 6H), 1.29 (d, 6H), 2.81 (m, 1H), 4.72 (m, 1H), 6.53 (dd, 1H), 6.29 (d, 1H), 6.97 (s, 1H), 7.50 (s, 1H), 7.53 (s, 1H), 8.11 (s, 1H), 8.18 (s, 1H).

El ácido 2-(3-isopropoxi-5-formil)benzoil aminotiazol-5-carboxílico requerido se preparó de acuerdo con el procedimiento dado bajo Ejemplo Z (Ruta 24); véase Ejemplo II₈₉.

EJEMPLO BB

2-[3-isopropoxi-5-(4-metil-1-piperidinocarbonilmetilenoxi) benzoil aminotiazol.

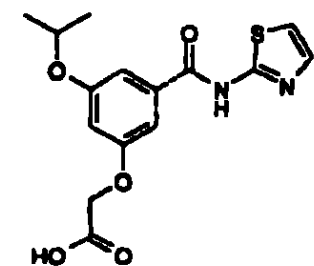
(Ruta 26)



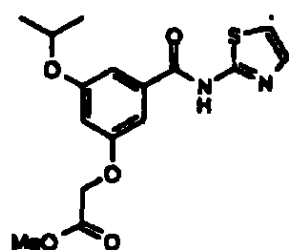
Éste se preparó por un acoplamiento de cloruro de ácido estándar (Ejemplo

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+2

A, Ruta 1), a partir de 2-(3-isopropoxi-5-carboximetilen oxi) benzoil aminotiazol, para producir el compuesto del título, ^1H NMR δ (d_6 -DMSO): 1.28 (d, 6H), 2.18 (s, 3H), 2.24 (m, 2H), 2.32 (m, 2H), 3.44 (ap t, 4H), 4.65 (m, 1H), 4.85 (s, 2H), 6.68 (ap t, 1H), 7.19 (m, 1H), 7.24 (ap d, 2H), 7.55 (ap d, 1H), 12.45 (bs, 1H); m/z 419 ($M+H$) $^+$ 417 ($M-H$) $^-$

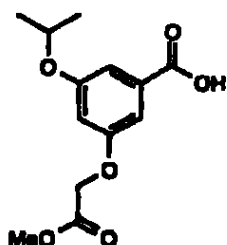


El 2-(3-isopropoxi-5-carboximetilen oxi) benzoil aminotiazol requerido se preparó de 2-(3-isopropoxi-5-metoxycarbonilmetilen oxi) benzoil aminotiazol por hidrólisis de éster estándar (Ruta 2a); ^1H NMR δ (d_6 -DMSO): 1.28 (d, 6H), 4.69 (m, 1H), 4.73 (s, 2H), 6.66 (ap t, 1H), 7.22 (s, 1H), 7.27 (ap d, 2H), 7.53 (ap d, 1H); m/z 337.31 ($M+H$) $^+$ 335.27 ($M-H$) $^-$



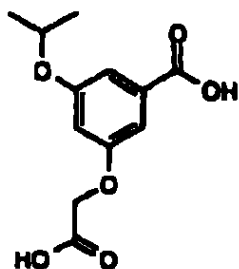
El material inicial requerido ácido 2-(3-isopropoxi-5-metoxycarbonilmetilen oxi) benzoil aminotiazol se preparó de 3-isopropoxi-5-(metoxycarbonil)metoxibenzoico y 2-aminotiazol (rendimiento aislado 48%) por un acoplamiento de cloruro de ácido estándar (Ruta 1); ^1H NMR δ (d_6 -DMSO): 1.27 (d, 6H), 3.70 (s, 3H), 4.71 (m, 1H), 4.86 (s, 2H), 6.99 (t, 1H), 7.23 (t, 1H), 7.26-7.27 (m, 2H), 12.53 (s, 1H); m/z 351.31 ($M+H$) $^+$, 349.28 ($M-H$) $^-$.

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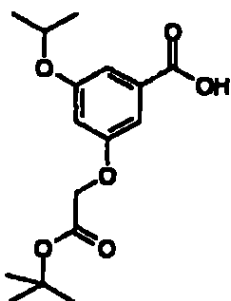


El material inicial requerido se preparó de ácido 3-isopropoxi-5-(metoxicarbonil metilen oxi) benzoico se preparó por monoesterificación de ácido 3-isopropoxi-5-(carboximetilen oxi) benzoico (rendimiento aislado 78%) usando las condiciones de Ram y Charles, *Tetrahedron* 1997, 53 (21), páginas 7335-7340: ^1H NMR δ (d_6 -DMSO): 1.25 (d, 6H), 3.69 (s, 3H), 4.65 (m, 1H), 4.83 (s, 2H), 6.71 (ap t, 1H), 6.98 (s, 1H), 7.01 (s, 1H), 12.97 (bs, 1H); m/z 554.27 ($2\text{M}+\text{NH}_4$) $^+$, 267.26 ($\text{M}-\text{H}$) $^-$

Ácido 3-isopropoxi-5-(carboximetoxi)benzoico



El compuesto del título se preparó de (3-isopropoxi-5-(t-butiloxilcarbonil)metoxi)benzoato de metilo (rendimiento aislado 56%) usando el método de hidrólisis estándar 2a. ^1H NMR δ (d_6 -DMSO): 1.25 (d, 6H), 4.62 (m, 1H), 4.69 (s, 2H), 6.67 (ap t, 1H), 6.96 (s, 1H), 7.02 (s, 1H), 12.95 (bs, 1H); m/z 253.27 ($\text{M}-\text{H}$) $^-$.



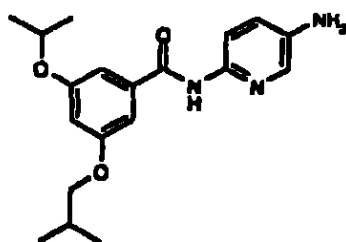
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El (3-isopropoxi-5-(t-butiloxilcarbonil)metoxi)benzoato de metilo requerido se preparó de acuerdo con el Método de Alquilación genérico B. Los datos analíticos de todos los intermedios fueron consistentes con las estructuras propuestas.

EJEMPLO CC

3-amino-6-(3-isobutiloxi-5-isopropiloxi benzoil) aminopiridina

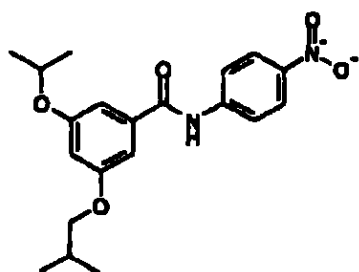
(Ruta 7b)



A una solución de 2-(3-isobutoxi-5-isopropoxibenzoil)amino-5-nitropiridina (1.74g, 4.66mmol) en etanol (20ml) se agregó 10% Pd/C bajo una atmósfera inerte. La mezcla de reacción se puso bajo una atmósfera de nitrógeno y se agitó vigorosamente durante 16 horas. La mezcla de reacción se inundó con argón, y luego se diluyó con agua (20ml) y se acidificó con 2M HCl (5ml). La suspensión se filtró a través de celita, y el filtrado se evaporó *in vacuo*. El residuo se dividió en porciones entre acetato de etilo (25ml) y bicarbonato de sodio saturado (25ml), y el extracto orgánico se secó sobre MgSO₄. La evaporación *in vacuo* proporcionó el compuesto del título como un sólido marrón (1.30g, 81%).

¹H NMR δ (d₆-DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.00 (m, 1H), 3.78 (d, 2H), 4.69 (m, 1H), 5.12 (s, 2H), 6.58 (t, 1H), 6.99 (dd, 1H), 7.1 (ap d, 2H), 7.73-7.78 (m, 2H), 10.24 (bs, 1H); m/z 344.41 (M+H)⁺

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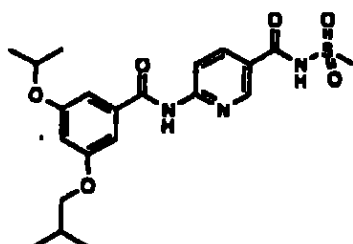


La 2-(3-isobutiloxi-5-isopropiloxi) benzoil amino-5-nitropiridina requerida se preparó de acuerdo con Ruta 1 (véase Ejemplo 10 en la tabla Piridina); ^1H NMR δ (d_6 -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 2.01 (m, 1H), 3.60 (d, 2H), 4.71 (m, 1H), 6.67 (ap t, 1H), 7.17 (ap d, 2H), 8.39 (d, 1H), 8.63 (dd, 1H), 9.20 (d, 1H), 11.43 (bs, 1H); m/z 374 ($M+H$) $^+$, 372 ($M-H$) $^-$.

EJEMPLO DD

2-[(3-isobutiloxi-5-isopropiloxi) benzoil] amino-5-(N-metilsulfonil)-carboxamido piridina

(Ruta 27)



Ácido 2-[(3-isobutiloxi-5-isopropiloxi) benzoil] aminopiridin-5-carboxílico (95mg, 0.255mmol) se agitó con EDC (59mg, 0.306mmol), DMAP (37mg, 0.306mmol) y metanosulfonamida (36mg, 0.378mmol) en DCM (3ml) bajo una atmósfera inerte durante 16 horas. La mezcla de reacción se diluyó con más DCM (10ml) y se extrajo con agua (2x5ml), 1M ácido cítrico (5ml) y salmuera (5ml). La filtración a través de una membrana PTFE y evaporación *in vacuo* proporcionó el compuesto del título como un sólido cristalino incoloro (90mg, 79%). ^1H NMR δ (d_6 -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.03 (m, 1H), 3.01 (s, 3H), 3.79 (d, 2H), 4.70 (m, 1H), 6.63 (ap t, 1H), 7.14 (ap d, 2H), 7.70 (dd, 1H), 8.12 (d, 1H), 8.34 (ap d, 1H), (9.83, s, 1H), 10.81 (bs, 1H); m/z 422.37 ($M+H$) $^+$, 420.30 ($M-H$) $^-$.

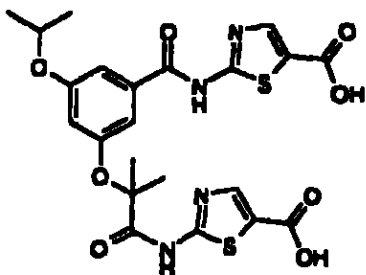
18/2/03

El material inicial ácido 2-[(3-isobutiloxi-5-isopropiloxi) benzoil] aminopiridin-5-carboxílico requerido se preparó de 2-[(3-isobutiloxi-5-isopropiloxi) benzoil] aminopiridin-5-carboxilato de metilo por hidrólisis estándar (Ruta 2a);

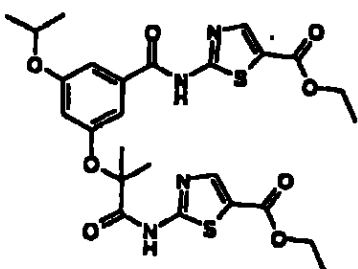
The requisite metil 2-(3-isobutiloxi-5-isopropiloxi) benzoil aminopiridine-5-carboxilate se preparó by standard acid cloruro coupling (Ruta 1);

EJEMPLO EE

Ácido 2-{3-isopropiloxi-5-[1-metil-1-(5-carboxi-tiazol-2-il aminocarbonil)] etoxi benzoil} aminotiazol-5-carboxílico
(Ruta 28)

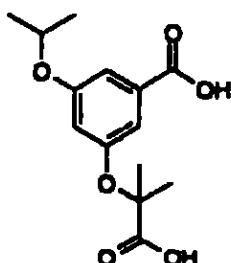


2-{3-Isopropiloxi-5-[1-metil-1-(5-etoxicarbonil-tiazol-2-il aminocarbonil)]etoxi benzoil} aminotiazol-5-carboxilato de etilo se hidrolizó por un método estándar de acuerdo con Ejemplo B Ruta 2a para producir ácido 2-{3-isopropiloxi-5-[1-metil-1-(5-carboxi-tiazol 2-il aminocarbonil)] etoxi benzoil} aminotiazol-5-carboxílico, ^1H NMR δ (d_6 -DMSO): 1.22 (d, 6H), 1.61 (s, 6H), 4.58-4.64 (m, 1H), 6.62 (s, 1H), 7.19 (s, 1H), 7.40 (s, 1H), 8.05 (s, 1H), 8.12 (s, 1H), m/z 533 (M-H) $^-$.



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El material inicial requerido 2-{3-isopropiloxi-5-[1-metil-1-(5-etoxicarbonil-tiazol-2-il aminocarbonil)] etoxi benzoil) aminotiazol-5-carboxilato de etilo se preparó por un método estándar de cloruro de ácido de acuerdo con Ejemplo A Ruta 1, partiendo de ácido 3-isopropiloxi-5-[(1-metil-1-carboxi) etoxi] benzoico.



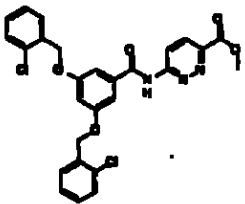
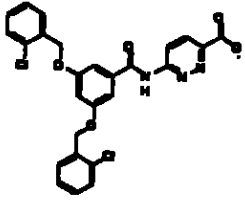
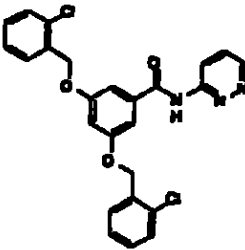
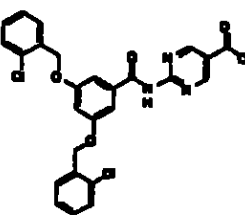
El material inicial requerido ácido 3-isopropiloxi-5-[(1-metil-1-carboxi) etoxi] benzoico se preparó de acuerdo con el procedimiento descrito por Corey y colegas, JACS 91 página 782 (1969), a partir de 3-isopropiloxi-5-hidroxi benzoato de metilo. El éster de metilo se hidrolizó bajo las condiciones de reacción, y el producto se aisló por extracción en solución de bicarbonato de sodio acuoso seguida por acidificación y extracción en acetato de etilo. Los extractos orgánicos se secaron (MgSO₄), se filtraron y se concentraron *in vacuo* para producir el producto crudo como un sólido amarillo pálido. La recristalización a partir de hexano produjo el compuesto del título como un sólido incoloro; ¹H NMR δ (d₆-DMSO): 1.15 (d, 6H), 1.5 (s, 6H), 4.55 (hept, 1H), 6.55 (dd, 1H), 6.95 (m, 1H), 7.05 (m, 1H), 13.0 (br s. 1H); m/z 283 (M+H)⁺, 281 (M+H)⁻.

EJEMPLO FF:

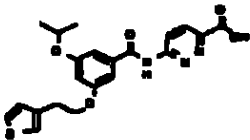
Por métodos análogos a los descritos más arriba se elaboraron también los siguientes compuestos de piridazina, los Ejemplos número FF₁ a FF₅.

Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
1		1			¹ H NMR d (d ₆ -DMSO): 3.95 (3H, s); 5.25 (4H, s); 6.95

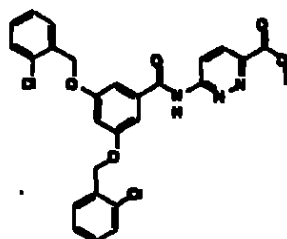
189188

Ejemplo	Estructura	Ruta	(M+H) ⁺	(M+H) ⁺	NMR
					(1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.65 (2H, m); 8.25 (1H, d); 8.6 (1H, d); 11.85 (1H, br s).
2		2	524/ 526		1H NMR δ (d6-DMSO): 2.0 (1H, s); 5.25 (4H, s); 6.95 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.25 (1H, d); 8.55 (1H, d); 11.8 (1H, br s). MS y NMR contenían señales debidas al material inicial ácido (~20 mol%); NMR contenía señales debido a acetato de etilo, (~33 mol%)
3		1			1H NMR δ (d6-DMSO): 5.24 (4H, s); 6.93 (1H, m); 7.37 (6H, m); 7.50 (2H, m); 7.61 (2H, m); 7.71 (1H, dd); 8.36 (1H, d); 9.00 (1H, d).
4		2*	524/ 526	522/ 524	1H NMR δ (d6-DMSO): 5.2 (4H, s); 6.95 (1H, m); 7.15 (1H, s); 7.3 (1H, d); 7.4 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 9.1 (2H, s); 11.35 (1H, br s); el espectro contiene además señales debido al material inicial ácido (~40 mol%)
5		2a, 1c (c)	428		δH (300MHz, DMSO-d6) 1.29 (6H, d), 3.08 (2H, t), 4.30 (2H, t),

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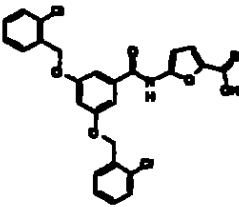
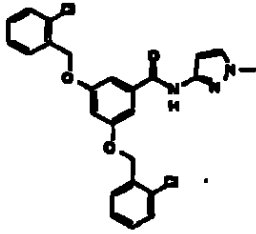
Ejemplo	Estructura	Ruta	MI-II	MI-III	NMR
					4.74 (1H, m), 6.73 (1H, s), 7.13 (1H, m), 7.24 (1H, s), 7.27 (1H, s), 7.34 (1H, m), 7.52 (1H, m), 8.25 (1H, d), 8.56 (1H, d), 11.75 (1H, s), 13.66 (1H, br s).

* Por Ejemplo 15, el intermedio de éster se preparó por ruta 1 y se ejemplifica como Ejemplo 12:

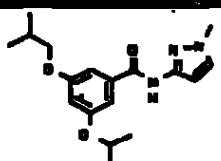
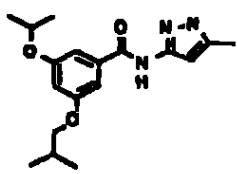
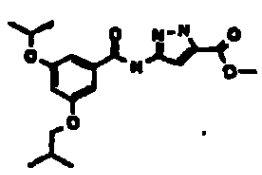
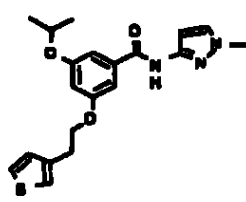
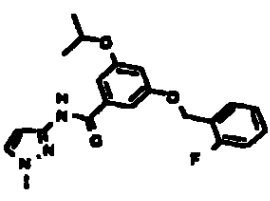


EJEMPLO GG:

Por métodos análogos a los descritos más arriba se elaboraron también los siguientes compuestos, Ejemplos números GG₁ a GG₇.

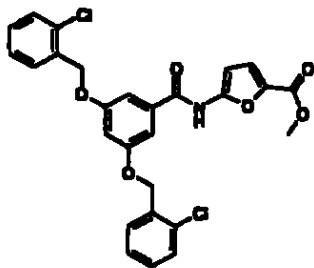
Ejemplo	Estructura	Ruta	MI-II	MI-III	NMR
1		2*			1H NMR d (d6-DMSO): 5.22 (4H, s); 6.54 (1H, d); 6.93 (1H, d); 7.27 (1H, d); 7.32-7.44 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 11.85 (1H, s); 12.86 (1H, br s).
2					1H NMR d (d6-DMSO): 3.75 (3H, s); 5.21 (4H, s); 6.55 (1H, d); 6.86 (1H, m); 7.31 (1H, m); 7.38 (4H, m); 7.38 (2H, m); 7.56 (1H, m); 7.59 (2H, m); 10.80 (1H, br s).
3		1a	331		

79/120

Ejemplo	Estructura	Ruta	ΔH-H ₂ O	ΔH-H ₂ O	NMR
					
4		1a	332.53	330.51	δ _H (300MHz, CDCl ₃) 1.02 (6H, d), 1.36 (6H, d), 2.08 (1H, m), 2.30 (3H, s), 3.75 (d, 2H), 4.60 (1H, hept), 6.66 (2H, m), 7.08 (2H, m), 9.85 (1H, br s).
5		1a	376.47	374.45	δ _H (300MHz, DMSO-d ₆) 0.98(6H, d), 1.27 (6H, d), 2.02 (1H, m), 3.80 (2H, d), 3.84 (3H, s), 4.68 (1H, hept), 6.62 (1H, s), 7.12 (3H, m), 10.95 (1H, br s), 13.65 (1H, br s).
6		1b (HA TU)	386.47		δ _H (300MHz, CDCl ₃) 1.35 (6H, d), 3.13 (2H, t), 3.72 (3H,s), 4.16 (2H, t), 4.53 (1H, hept), 6.60 (1H, s), 6.83 (1H, s), 7.00 (4H, m), 7.28 (2H, m), 8.98 (1H, br s).
7			384		

* Para GG₁, el intermedio éster se preparó por ruta 1:

Fig 1a



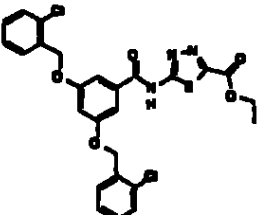
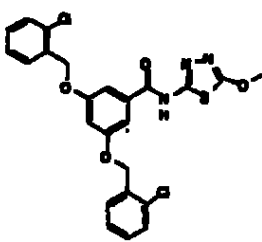
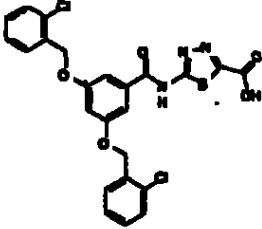
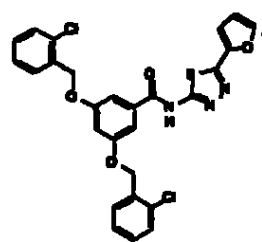
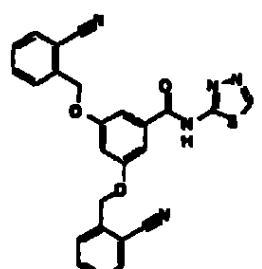
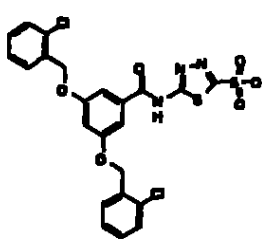
¹H NMR δ (d₆-DMSO): 3.80 (3H, s); 5.23 (1H, m); 6.61 (1H, d); 6.95 (1H, s); 7.33-7.43 (7H, m); 7.50-7.55 (2H, m); 7.60-7.63 (2H, m); 11.90 (1H, br s).

EJEMPLO HH:

Por métodos análogos a los descritos más arriba se elaboraron también los siguientes compuestos, Ejemplos números HH₁ a HH₃₃.

Ejemplo	Estructura	Ruta	CMR-13C	CMR-15N	NMR
1	<chem>COc1cc2c(c1)oc(=O)nc2C(=O)Oc3cc(OCc4ccccc4Cl)cc(OCc5ccccc5Cl)c3</chem>	1	484		¹ H NMR d (d ₆ -DMSO): 5.26 (4H, s); 7.02 (1H, s); 7.40 (4H, m); 7.46 (2H, m); 7.54 (2H, m); 7.63 (2H, m); 9.24 (1H, s); 13.08 (1H, br s).
2	<chem>COc1cc2c(c1)oc(=O)nc2C(=O)Oc3cc(OCc4ccccc4Cl)cc(OCc5ccccc5Cl)c3</chem>	1			¹ H NMR d (d ₆ -DMSO): 2.63 (3H, s); 5.24 (4H, s); 6.96 (1H, s); 7.35-7.45 (6H, m); 7.51 (2H, m); 7.61 (2H, m); 12.84 (1H, br s).
3	<chem>COc1cc2c(c1)oc(=O)nc2C(=O)Oc3cc(OCc4ccccc4Cl)cc(OCc5ccccc5Cl)c3</chem>	1			¹ H NMR d (d ₆ -DMSO): 1.38 (3H, t), 3.25 (2H, q); 5.25 (4H, s); 6.97 (1H, s); 7.41 (6H, m); 7.54 (2H, m); 7.64 (2H, m); 13.13 (1H, br s).
4		1			¹ H NMR d (d ₆ -DMSO)

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Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
					1.32 (3H, t), 4.32 (2H, q); 5.20 (4H, s); 6.78 (1H, s); 7.39(4H, m); 7.46 (2H, m); 7.53 (2H, m); 7.64 (2H, m).
5		1			¹ H NMR d (d6-DMSO): 4.20 (3H, s); 5.28 (4H, s); 6.98 (1H, s); 7.42 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 12.78 (1H, br s).
6		2	530, 532		¹ H NMR d (d6-DMSO): 5.24 (4H, s); 6.96 (1H, s); 7.37 (4H, m); 7.33 (2H, m); 7.53 (2H, m); 7.62 (2H, m).
7		1			¹ H NMR d (d6-DMSO): 5.25 (4H, s); 6.74 (1H, m); 6.99 (1H, s); 7.23 (1H, m); 7.41 (4H, m); 7.49 (2H, m); 7.53 (2H, m); 7.65 (2H, m); 7.97 (1H, s); 13.20 (1H, br s).
8		1			¹ H NMR d (d6-DMSO): 5.34 (4H, s); 7.03 (1H, s); 7.49 (2H, m); 7.57 (2H, m); 7.75 (4H, m); 7.91 (2H, d); 9.22 (1H, s); 13.06 (1H, br s).
9		19		564, 566	¹ H NMR d (d6-DMSO): 5.20 (4H, s); 6.68 (1H, m); 7.37 (4H, m); 7.45 (2H, m); 7.50 (2H, m); 7.62 (2H, m).

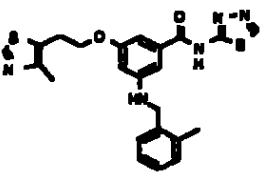
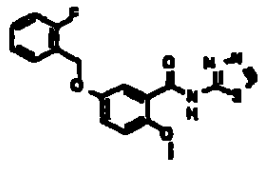
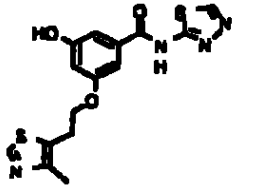
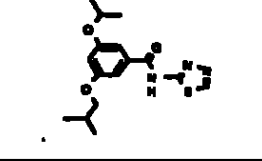
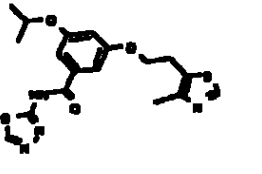
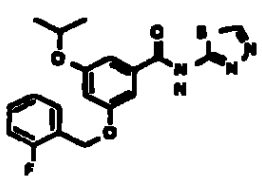
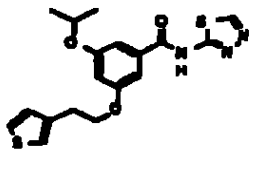
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Ejemplo	Estructura	Ruta	MS-TOF	MS-MS	NMR
10		1	566	564, 566	¹ H NMR d (d6-DMSO): 5.22 (4H, s); 6.99 (1H, m); 7.39 (4H, m); 7.45 (2H, m); 7.51 (2H, m); 7.60 (2H, m); 13.34 (1H, br s).
11		1			¹ H NMR d (d6-DMSO): 2.33 (3H, s), 2.37 (3H, s); 3.25 (2H, m); 4.21 (2H, t); 5.14 (2H, s); 6.84 (1H, m); 7.22 (3H, m); 7.31 (1H, s); 7.40 (2H, m); 8.83 (1H, s); 9.21 (1H, s); 12.99 (1H, br s).
12		1			¹ H NMR d (d6-DMSO): 1.33 (3H, t); 2.32 (3H, s), 2.35 (3H, s); 3.22 (2H, m); 4.21 (2H, t); (2H, q); 5.13 (2H, s); 6.87 (1H, m); 7.22 (3H, m); 7.33 (1H, m); (2H, m); 8.82 (1H, s); 13.46 (1H, br s).
13				516, 518	¹ H NMR d (d6-DMSO): 5.21 (4H, s); 6.98 (1H, m); 7.34-7.40 (6H, m); 7.50 (2H, m); 7.59 (2H, m).
14			398		¹ H NMR δ (d6-DMSO): 1.0 (d, 6H), 2.0 (hept, 1H), 2.35 (s, 3H), 3.8 (d, 2H), 5.2 (s, 2H), 6.85 (d, 1H), 7.15-7.25 (m, 3H), 7.30 (d, 1H), 7.4 (2H, m), 9.2 (s, 1H), 11.6 (br s, 1H).
15			402		¹ H NMR δ (d6-DMSO): 1.0 (d, 6H), 2.0 (hept, 1H), 3.8 (d, 2H), 5.2 (s, 2H), 6.85 (s, 1H), 7.2-7.3 (m, 2H), 7.35 (s, 1H), 7.4 (m, 2H), 7.6 (t, 1H), 9.2 (s, 1H), 13.0 (br s, 1H).

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Ejemplo	Estructura	Ruta	(M-H) ⁻	(M+H) ⁺	NMR
16			350		
17			322		¹ H NMR δ (d ₆ -DMSO): 1.3 (d, 12H), 4.7 (hept, 2H), 6.65 (s, 1H), 7.25 (s, 2H), 9.2 (s, 1H), 12.95 (br s, 1H)
18					¹ H NMR δ (d ₆ -DMSO): 2.34 (s, 3H), 3.23 (t, 2H), 4.21 (t, 2H), 4.62 (d, 2H), 5.26 (d, 1H), 5.40 (d, 1H), 6.05 (m, 1H), 6.75 (s, 1H), 7.31 (s, 2H), 8.83 (s, 1H), 9.20 (s, 1H), 12.48 (br s, 1H).
19					¹ H NMR δ (d ₆ -DMSO): 2.31 (s, 3H), 2.34 (s, 1H), 3.22 (t, 2H), 4.21 (t, 2H), 5.13 (s, 2H), 6.84 (s, 1H), 7.15-7.25 (m, 1H), 7.26 (1H, m), 7.39 (2H, m), 8.81 (s, 1H).
20					¹ H NMR δ (d ₆ -DMSO): 2.37 (s, 3H), 2.42 (s, 3H), 3.29 (t, 2H), 4.29 (t, 2H), 5.21 (s, 2H), 5.58 (s, 2H), 6.92 (s, 1H), 7.22-7.31 (m, 3H), 7.40 (1H, bs), 7.47 (2H, m), 8.90 (s, 1H). MS ES ⁺ 547.2, 549.1 (M+H) ⁺
21		19			¹ H NMR δ (d ₆ -DMSO): 2.35 (s, 3H), 2.93 (s, 6H), 3.22 (m, 2H), 4.19 (m, 2H), 6.41 (m, 1H), 6.98 (m, 1H), 7.06 (m, 1H), 8.80 (s, 1H), 9.17 (s, 1H).
22		19			¹ H NMR δ (d ₆ -DMSO): 2.58 (m, 6H), 3.43 (t,

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Ejemplo	Estructura	Ruta	ME (g)	ME (H)	NMR
					¹ H), 4.37 (t, 2H), 4.50 (d, 2H), 6.41 (m, 1H), 6.61 (m, 1H), 7.16 (m, 2H), 7.34-7.45 (m, 3H), 7.50 (m, 1H), 9.05 (s, 1H), 9.42 (s, 1H).
23		1	358		¹ H NMR δ (d ₆ -DMSO): 3.81 (s, 3H), 5.15 (s, 2H), 7.18 (t, 1H), 7.2-7.3 (m, 3H), 7.38 (d, 1H), 7.39-7.43 (m, 1H) 7.55 (t, 1H), 12.27 (br s, 1H)
24		20	363	361	¹ H NMR δ (d ₆ -DMSO): 2.35 (s, 3H), 3.2 (t, 2H), 4.2 (t, 2H), 6.55 (m, 1H), 7.05 (s, 1H), 7.2 (s, 1H), 8.81 (s, 1H), 9.2 (s, 1H), 9.8 (br s, 1H).
25		1b	336		
26		1b	405		
27		2a, 1c (b)	388	386	δ _H (500MHz, DMSO-d ₆) 1.27 (6H, d), 4.73 (1H, m), 5.21 (2H, s), 6.82 (1H, s), 7.20-7.31 (3H, br m), 7.36-7.47 (2H, br m), 7.58 (1H, t), 9.23 (1H, s), 12.97 (1H, br s).
28		2a, 1c (b)	389		δ _H (500MHz, DMSO-d ₆) 1.28 (6H, d), 3.06 (2H, t), 4.27 (2H, t), 4.72 (1H, m), 6.72 (1H, s), 7.12 (1H, d), 7.26 (1H, s), 7.31 (2H, m), 7.48 (1H, m), 9.20 (1H, s)
29		2a, 1a (d)	434		δ _H (300MHz, DMSO-d ₆) 1.26 (6H, d), 3.07 (2H, t), 4.15 (2H, t), 4.70 (1H,

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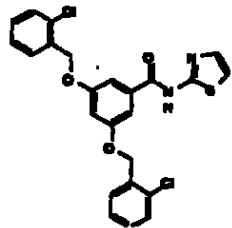
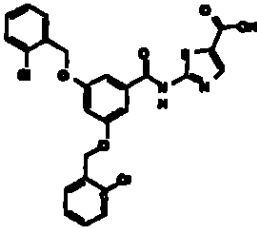
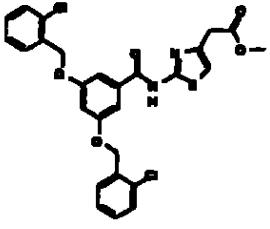
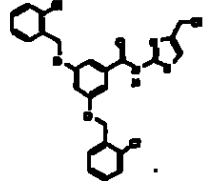
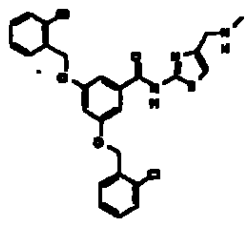
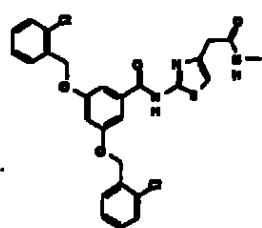
Ejemplo	Estructura	Ruta	(M.F.)	(M.F.)	NMR
					m), 6.68 (1H, s), 7.11 (1H, d), 7.22- 7.34 (3H, br m), 7.47 (1H, br s).
30		1b (HA TU)	402. 42	400. 39	δ_H (300MHz, DMSO- d_6) 1.27 (6H, d), 2.63 (3H, s), 4.70 (1H, hept), 5.20 (2H, s), 6.82 (1H, s), 7.24 (3H, m), 7.39 (2H, m), 7.56 (1H, t), 12.80 (1H, br s).
31		1b (HA TU)	440. 40	402. 37	δ_H (300MHz, DMSO- d_6) 1.27 (6H, d), 2.63 (3H, s), 3.06 (2H, t), 4.25 (2H, t), 4.70 (1H, hept), 6.72 (1H, s), 7.12 (1H, d), 7.28 (3H, m), 7.47 (1H, m), 12.77 (1H, br s).
32		1b (HA TU)	468. 39	466. 37	δ_H (300MHz, DMSO- d_6) 2.63 (3H, s), 5.23 (4H, s), 6.97 (1H, s), 7.24 (4H, m), 7.43 (4H, m), 7.57(2H, t), 12.84 (1H, br s).
33		1a	336. 44	334. 40	

EJEMPLO II:

También se prepararon por métodos análogos a los descritos más arriba los siguientes compuestos, Ejemplos números II₁ a III₁₆₆. Algunos compuestos se prepararon por Ruta 1b (síntesis multi-paralela), como se describe en Ejemplo T. Para compuestos elaborados por Ruta 2a (hidrólisis de ésteres), los materiales iniciales requeridos pueden prepararse por Ruta 1 ó 1b.

Ejemplo	Estructura	Ruta	(M.F.)	(M.F.)	NMR
1		1	485,		¹ H NMR d (d6-DMSO):

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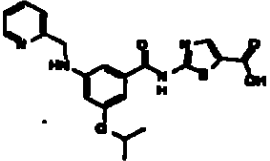
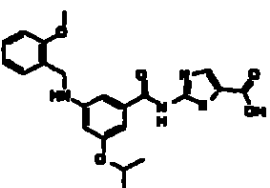
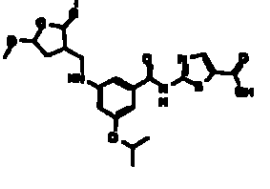
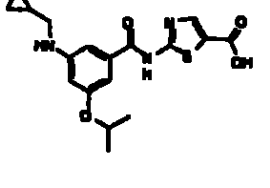
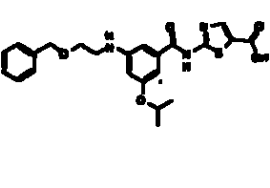
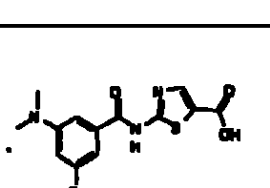
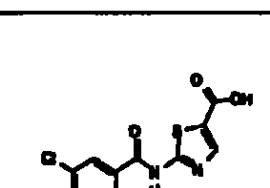
Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
			487		5.24 (4H, s); 6.93 (1H, s); 7.26 (1H, d); 7.36-7.43 (6H, m); 7.50 (2H, m); 7.55 (1H, d); 7.61 (2H, m); 12.60 (1H, br s).
2		2a *****			1H NMR d (d6-DMSO): 5.25 (4H, s); 7.0 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.2 (1H, d).
3		1			1H NMR d (d6-DMSO): 3.62 (3H, s); 3.76 (2H, s); 5.24 (4H, s); 6.94 (1H, m); 7.06 (1H, s); 7.38-7.47 (6H, m); 7.54 (2H, m); 7.63 (2H, m); 12.69 (1H, br s).
4		1		531	1H NMR d (d6-DMSO): 4.77 (2H, s); 5.25 (4H, s); 6.94 (1H, m); 7.31 (1H, s); 7.36-7.48 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 12.83 (1H, br s) (+ 0.4 eq. iPr2NEt).
5		3	528, 530		1H NMR d (d6-DMSO): 2.63 (3H, m); 4.16 (2H, m); 5.24 (4H, s); 6.99 (1H, s); 7.38-7.44 (7H, m); 7.52 (2H, m); 7.62 (2H, m); 9.06 (1H, br s); 12.75 (1H, br s).
6		3			1H NMR d (d6-DMSO): 2.57 (3H, m); 3.48 (2H, m); 5.25 (4H, s); 6.95 (2H, m); 7.36-7.44 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 7.83 (1H, m); 12.60 (1H, br s).
7		2a *****		497, 499 (-CO2)	1H NMR d (d6-DMSO): 3.64 (2H, s); 5.26 (4H, s); 6.95 (1H, s); 7.04 (1H, s); 7.37-7.46 (6H, m); 7.54 (2H, m); 7.63 (2H, m); 12.40 (1H, br s).

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Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
					s); 12.68 (1H, br s) (.HCl).
8		2a ****		459, 415 (- CO2)	¹ H NMR d (d6-DMSO): 5.15 (4H, s); 6.9 (1H, s); 7.2-7.5 (12H, m); 8.1 (1H, s).
9		1			¹ H NMR d (d6-DMSO): (iPr2NEt salt) 1.24 (15H, m); 3.12 (2H, m); 3.80 (2H, m); 5.24 (4H, s); 6.93 (1H, m); 7.36-7.45 (7H, m); 7.51 (2H, m); 7.61 (2H, m); 12.56 (1H, br s).
10		3			¹ H NMR d (d6-DMSO): 2.45 (4H, m); 3.55 (2H, s); 3.61 (4H, m); 5.29 (4H, s); 7.00 (1H, m); 7.11 (1H, s); 7.43-7.51 (6H, m); 7.58 (2H, m); 7.67 (2H, m); 12.66 (1H, br s).
11		4	550, 552		¹ H NMR d (d6-DMSO): 5.19 (2H, br s); 5.23 (4H, s); 6.72 (1H, dd); 6.93 (1H, m); 7.03 (1H, m); 7.35-7.44 (7H, m); 7.51 (2H, m); 7.61 (2H, m); 12.46 (1H, br s).
12		3	558, 560		¹ H NMR d (d6-DMSO): 2.60 (2H, t); 3.45 (2H, t); 3.72 (2H, s); 5.22 (4H, s); 6.91 (1H, m); 6.96 (1H, s); 7.35-7.30 (7H, m); 7.50 (2H, m); 7.60 (2H, m).
13		3	586, 588		¹ H NMR d (d6-DMSO): 3.11 (2H, q); 3.37 (2H, q); 3.50 (2H, s); 3.61 (1H, t); 5.22 (4H, s);

Templo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
					6.92 (2H, m); 7.34-7.42 (6H, m); 7.49 (2H, m); 7.60 (2H, m); 7.88 (1H, br s).
14		3	554, 556		¹ H NMR d (d ₆ -DMSO): 0.29 (2H, m); 0.40 (2H, m); 2.16 (1H, m); 3.79 (2H, s); 5.27 (4H, s); 6.98 (2H, m); 7.40-7.48 (7H, m); 7.56 (2H, m); 7.66 (2H, m).
15		2b ****	366	364	¹ H NMR d (d ₆ -DMSO): 7.05 (1H, d); 7.35 (1H, t); 7.45 (1H, dd); 7.6-7.75 (2H, m); 7.85 (1H, m); 7.9-8.0 (2H, m); 8.15 (1H, s); 13.1 (2H, br s).
16		6			¹ H NMR d (d ₆ -DMSO): 2.68 (3H, s); 3.81 (1H, s); 5.15 (2H, s); 6.38 (1H, s); 6.87 (1H, s); 7.00 (1H, s); 7.37 (2H, m); 7.49 (1H, m); 7.58 (1H, m); 8.10 (1H, s); 8.21 (1H, s).
17		6			¹ H NMR d (d ₆ -DMSO): 1.32 (6H, d); 4.88 (1H, m); 7.87 (1H, s); 8.05 (1H, s); 8.14 (1H, s); 8.45 (1H, s).
18		6		400, 402) CO ₂)	¹ H NMR d (d ₆ -DMSO): 1.22 (6H, d); 4.36 (2H, m); 4.58 (1H, m); 6.24 (1H, s); 6.47 (1H, m); 6.84 (2H, m); 7.26 (3H, m); 7.37 (2H, m); 7.45 (1H, m); 7.76 (1H, br s).
19		6			¹ H NMR d (d ₆ -DMSO): 1.21 (6H, d); 4.28 (2H, m); 4.55 (1H, m); 6.26 (1H, s); 6.43 (1H, m); 6.83 (1H, s); 6.89 (1H, s); 7.20 (1H, m); 7.26-7.37 (4H, m); 7.74 (1H, br s).
20		6		367	¹ H NMR d (d ₆ -DMSO):

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Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
				(- CO2)	¹ H NMR d (d ₆ -DMSO): 1.23 (6H, d); 4.38 (2H, s); 4.60 (1H, m); 6.33 (1H, m); 6.89 (2H, m); 7.47 (1H, dd); 7.89 8.51 (1H, dd); 8.63 (1H, d).
21		6		396 (- CO2)	¹ H NMR d (d ₆ -DMSO): 1.21 (6H, d); 3.81 (3H, s); 4.24 (2H, m); 4.55 (1H, m); 6.26 (2H, m); 6.84 (3H, m); 6.97 (1H, m); 7.20 (2H, m).
22		6		464, 420 (- CO2)	
23		6			¹ H NMR d (d ₆ -DMSO): 0.28 (2H, m); 0.52 (2H, m); 1.09 (1H, m); 1.32 (6H, d); 3.02 (2H, d); 4.69 (1H, d); 6.50 (1H, s); 6.99 (2H, s); 8.20 (1H, s)
24		6			¹ H NMR d (d ₆ -DMSO): 1.24 (6H, d); 3.29 (2H, m); 3.56 (2H, t); 4.50 (2H, s); 4.58 (1H, m); 6.37 (1H, m); 6.85 (1H, s); 6.90 (1H, s); 7.26 (2H, m); 7.13 (3H, m); 8.10 (1H, s).
25		6		348	¹ H NMR d (d ₆ -DMSO): 1.27 (6H, d); 2.96 (6H, s); 4.69 (1H, m); 6.39 (1H, m); 6.97 (1H, s); 7.04 (1H, s); 8.13 (1H, s); 12.89 (1H, br s).
26		2a ****	389, 391		¹ H NMR d (d ₆ -DMSO): 5.21 (2H, s); 7.29-7.49 (6H, m); 7.74 (2H, s); 8.13 (1H, S); 13.1 (1H, br s).
27		1			¹ H NMR d (d ₆ -DMSO): 2.31 (3H, s); 2.35 (3H, s);

20201

Ejemplo	Estructura	Ruta	(M ₁ , H ₁)	(M ₂ , H ₂)	NMR
					s); 3.22 (2H, t); 4.21 (2H, t); 5.12 (2H, s); 6.79 (1H, m); 7.18-7.28 (4H, m); 7.30 (1H, m); 7.54 (1H, d); 8.82 (1H, s); 12.48 (1H, br s).
28		1			¹ H NMR d (d ₆ -DMSO): 2.32 (3H, s); 2.37 (3H, s); 3.24 (2H, t); 4.22 (2H, t); 5.13 (2H, s); 6.80 (1H, m); 7.19 (3H, m); 7.29 (1H, s); 7.37-7.45 (3H, m); 9.06 (1H, s); 12.48 (1H, br s).
29		1			¹ H NMR d (d ₆ -DMSO): (3H, t); 2.32 (3H, s); 2.37 (3H, s); 3.24 (2H, t); 4.14-4.29 (4H, m); 5.13 (2H, s); 6.84 (1H, m); 7.21 (4H, m); (1H, s); 7.38 (2H, m); 8.20 (1H, s); 8.81 (1H, s).
30		2a (1)			¹ H NMR d (d ₆ -DMSO): 1.26 (d, 6H), 4.69 (m, 1H), 5.14 (s, 2H), 6.75 (s, 1H), 7.26-7.48 (m, 7H), 8.01 (s, 1H).
31		2a (1b)			¹ H NMR d (d ₆ -DMSO): 1.0 (d, 12H), 2.0 (m, 2H), 3.8 (d, 4H), 6.75 (s, 1H), 7.25 (d, 2H), 8.15 (s, 1H).
32		1			¹ H NMR δ (d ₆ -DMSO): 1.26 (d, 6H), 4.69 (m, 1H), 5.16 (s, 2H), 6.74 (s, 1H), 7.26 (d, 1H), 7.31-7.47 (m, 7H), 8.54 (d, 1H), 12.47 (bs, 1H).
33		2a (1)			¹ H NMR δ (d ₆ -DMSO): 1.26 (d, 6H), 2.38 (s, 3H), 4.69 (m, 1H), 5.18 (s, 2H), 6.31 (s, 1H), 6.76 (s, 1H), 7.30 (s, 1H), 7.35

202
203

Ejemplo	Estructura	Ruta	(M-H) ⁻	(M-H) ⁺	NMR
					(s, 1H), 8.00 (s, 1H).
34		2a (1)			¹ H NMR δ (d ₆ -DMSO): 1.26 (d, 6H), 2.39 (s, 3H), 4.70 (m, 1H), 5.20 (s, 2H), 6.31 (s, 1H), 6.79 (s, 1H), (s, 1H), 7.32 (s, 1H), 8.12 (s, 1H).
35		1b	397		
36		1b	401		
37		1			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 2.39 (s, 3H), 4.69 (m, 1H), 5.18 (s, 2H), 6.31 (s, 1H), 6.76 (s, 1H), 7.26 (m, 2H), 7.32 (s, 1H), 8.53 (d, 1H).
36		2a (1)	379	377	¹ H NMR δ (d ₆ -DMSO): 12.98 (bs, 1H), 8.12 (s, 1H), 7.24 (s, 1H), 6.66 (s, 1H), 4.70 (m, 1H), 3.79 (d, 2H), 2.01 (m, 1H), 1.28 (d, 6H), 0.98 (d, 6H).
37		2a (1b)	365		¹ H NMR δ (d ₆ -DMSO): 1.25 (d, 12H), 4.7 (hept, 2H), 6.65 (s, 1H), 7.2 (s, 2H), 8.15 (s, 1H).

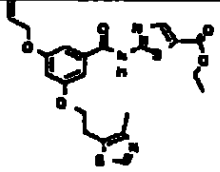
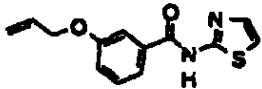
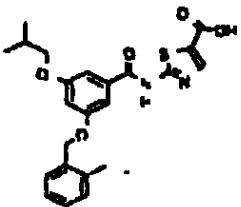
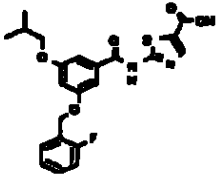
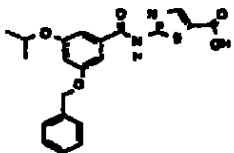
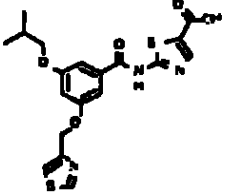
203
502

Ejemplo	Estructura	Ruta	(M.H.)	(M.H.)	NMR
38		2a (1)			¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.16 (s, 4H), 6.90 (s, 1H), 7.29-7.47 (m, 7H), 7.53 (s, 1H), 8.03 (m, 1H), 12.90 (bs, 1H).
39		2a (1)			¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.17 (s, 4H), 6.93 (s, 1H), 7.29-7.45 (m, 7H), 7.53 (s, 1H), 8.13 (m, 1H).
40		1			¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.14 (s, 4H), 6.90 (s, 1H), 7.26 (d, 1H), 7.31-7.47 (m, 7H), 7.49 (m, 1H), 7.55 (d, 1H), 12.56 (bs, 1H).
41		1b	349		
42		2a (1)			¹ H NMR δ (d ₆ -DMSO): 5.22 (s, 4H), 6.96 (s, 1H), 7.20-7.29 (m, 4H), 7.37-7.44 (m, 4H), 7.55 (m, 2H), 8.12 (s, 1H).
43		2a (1)			¹ H NMR δ (d ₆ -DMSO): 5.21 (s, 4H), 6.93 (s, 1H), 7.19-7.29 (m, 4H), 7.38-7.46 (m, 4H), 7.56 (m, 2H), 8.03 (s, 1H).
44		2a (1)			¹ H NMR δ (d ₆ -DMSO): 2.38 (s, 3H), 3.25 (t, 2H), 4.24 (t, 2H), 4.65 (d, 2H), 5.27 (d, 1H), 5.42 (d, 1H), 6.05 (m, 1H), 6.78 (s, 1H), 7.32 (s, 2H), 8.15 (s, 1H), 8.90 (s, 1H), 12.94

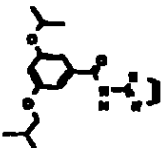
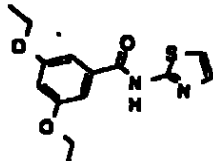
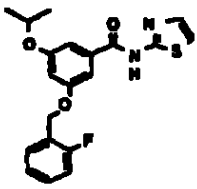
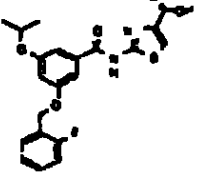
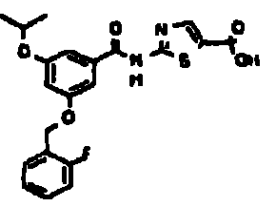
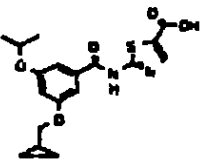
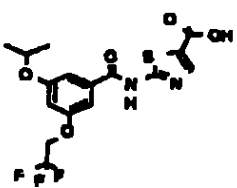
204
2

Ejemplo	Estructura	Ruta	MP (°C)	MP (°C)	NMR
					(br s, 1H).
45		2a (1)			¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.34 (s, 3H), 3.22 (t, 2H), 4.21 (t, 2H), 5.13 (s, 2H), 6.82 (s, 1H), 7.16-7.25 (m, 3H), 7.30 (1H, s), 7.39 (1H, m), 7.98 (s, 1H), 8.81 (s, 1H).
46		2a *	419	417	¹ H NMR δ (d ₆ -DMSO): 3.8 (s, 3H), 5.3 (s, 2H), 7.15 (dd, 1H), 7.2-7.4 (m, 4H), 7.5 (d, 1H), 7.6 (d, 1H), 8.0 (s, 1H).
47		2a *	427	425	¹ H NMR δ (d ₆ -DMSO): 1.1 (d, 6H), 2.85 (hept, 1H), 3.75 (s, 3H), 5.2 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (d, 1H), 8.0 (s, 1H).
48		2a **	405	403	¹ H NMR δ (d ₆ -DMSO): 2.34 (s, 3H), 3.20 (t, 2H), 4.13 (t, 2H), 6.43 (s, 1H), 6.92 (s, 1H), 6.97 (s, 1H), 8.09 (s, 1H), 8.83 (s, 1H), 12.75 (bs, 1H).
49		2a *			¹ H NMR δ (d ₆ -DMSO): 2.33 (s, 3H), 2.36 (2.36, 3H), 3.23 (t, 2H), 4.22 (t, 2H), 5.15 (s, 2H), 7.21 (s, 1H), 7.02-7.44 (m, 6H), 8.13 (s, 1H), 8.85 (s, 1H), 12.92 (bs, 1H).
50		6 **			¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.34 (s, 3H), 3.19 (t, 2H), 4.12 (t, 2H), 4.25 (s, 2H), 6.37 (s, 1H), 6.92 (d, 2H), 7.08-7.21 (m, 3H), 7.25 (dd, 1H), 8.10 (s, 1H), 8.8.5 (s, 1H), 12.76 (bs, 1H).
51		6 **			
52		1			¹ H NMR δ (d ₆ -DMSO): 1.28 (t, 3H), 2.35 (s, 3H),

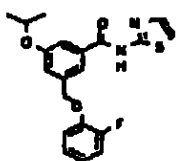
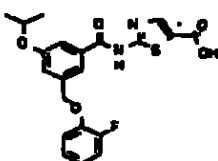
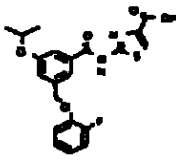
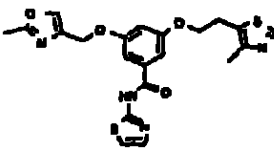
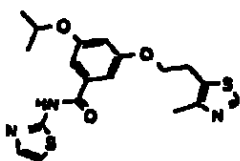
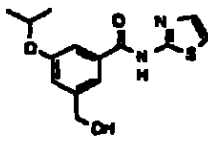
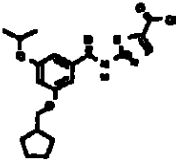
209

Ejemplo	Estructura	Ruta	(M+H) ⁺	(M-H) ⁻	NMR
					3.22 (t, 2H), 4.11 (t, 2H), 4.27 (q, 2H), 4.63 (d, 2H), 5.26 (dd, 1H), 5.39 (d, 1H), 6.04 (m, 1H), 6.76 (t, 1H), 7.28 (d, 2H), 8.21 (s, 1H), 8.81 (s, 1H), 13.02 (bs, 1H)
53		1b	261	259	¹ H NMR δ (CDCl ₃): 4.58 (d, 2H), 5.31 (dd, 1H), 5.45 (dd, 1H), 6.04 (m, 1H), 6.95 (d, 1H), 7.11 (d, 1H), 7.18 (m, 1H), 7.41 (t, 1H), 7.55 (m, 2H), 12.09 (br s, 1H).
54		2a	445		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.98-2.05 (m, 1H), 3.81 (d, 2H), 5.20 (s, 2H), 6.81 (s, 1H), 7.0-7.1 (m, 2H), 7.35 (s, 1H), 7.38-7.45 (m, 2H), 7.58 (t, 1H), 8.03 (s, 1H), 12.90 (br s, 1H).
55		2a	441		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H); 1.98-2.05 (m, 1H), 2.36 (s, 3H), 3.81 (d, 2H), 5.17 (s, 2H), 6.81 7.17-7.23 (m, 3H), 7.32 (s, 1H), 7.40 (ap d, 2H), 8.01 (s, 1H)
56		2a			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 4.71 (sept, 1H), 5.16 (d, 2H), 6.78 (d, 1H), 7.25-7.51 (m, 7H), 8.12 (s, 1H), 12.98 (bs, 1H)
57		1b	434	432	¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.98-2.05 (m, 1H), 3.81 (d, 2H), 5.26 (s, 2H), 6.83 (ap t, 1H), 7.30 (s, 1H), 7.39 (s, 1H), 7.79 (s, 1H), 8.12 (s, 1H), 9.1 (s, 1H).
58		1b	335		

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207

Ejemplo	Estructura	Ruta	(M.H)	(M.H)	NMR
					
59		1b	293		
60		1			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.74 (sept, 1H), 5.22 (s, 2H), 6.79 (t, 1H), 7.19-7.32 (m, 4H), 7.37 (t, 1H), 7.43 (m, 1H), 7.56 (m, 2H), 12.61 (bs, 1H)
61		2a			¹ H NMR δ (d ₆ -DMSO) 1.26 (d, 6H), 4.64-4.76 (m, 1H), 5.20 (s, 2H), 6.78 (s, 1H), 7.18-7.34 (m, 3H), 7.36-7.46 (m, 2H), 7.50-7.60 (m, 1H), 7.98 (s, 1H)
62		2a			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 4.71 (m, 1H), 5.20 (s, 2H), 6.78-6.84 (m, 1H), 7.18-7.31 (m, 3H), 7.34-7.49 (m, 2H), 7.52-7.61 (m, 1H), 8.12 (s, 1H), 12.98 (bs, 1H)
63		2a	377		¹ H NMR δ (d ₆ -DMSO): 0.0-0.2 (m, 2H), 0.22-0.3 (m, 2H), 0.98 (d, 6H), 3.59 (d, 2H), 4.35-4.42 (m, 1H), 6.4 (s, 1H), 6.93 (s, 2H), 7.82 (s, 1H).
64		2a	403		¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.78 (m, 1H), 4.86 (q, 2H), 6.89 (ap t, 1H), 7.36 (ap t, 2H), 8.17 (s, 1H), 13.05 (bs)

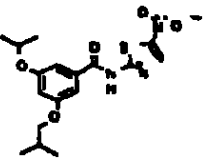
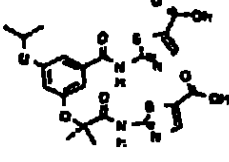
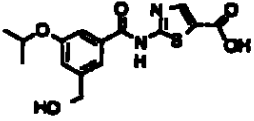
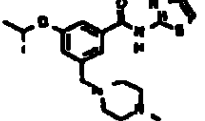
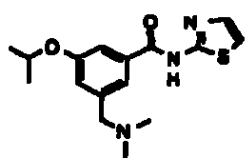
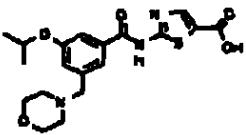
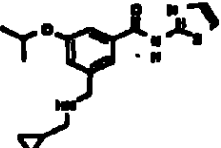
207
208

Ejemplo	Estructura	Ruta	MI (g)	MI (g)	NMR
65		1 ***			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.72 (m, 1H), 5.19 (s, 2H), 6.88-6.97 (m, 1H), 7.09 (m, 1H), 7.16-7.26 (m, 4H), 7.54 (d, 1H), 7.61 (s, 1H), 7.70 (s, 1H), 12.05 (bs, 1H).
66		2a ***			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.74 (m, 1H), 5.18 (s, 2H), 6.87-6.97 (m, 1H), 7.11 (m, 1H), 7.16-7.26 (m, 3H), 7.63 (s, 1H), 7.71 (s, 1H), 8.11 (s, 1H).
67		2a ***			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.74 (m, 1H), 5.18 (s, 2H), 6.89-6.97 (m, 1H), 7.09 (m, 1H), 7.17-7.26 (m, 3H), 7.66 (s, 1H), 7.74 (s, 1H), 7.99 (s, 1H).
68		1b	457		
69		1b	404		
70		23			¹ H NMR δ (d ₆ -DMSO): 1.28 (d, 6H), 4.51 (s, 2H), 4.71 (m, 1H), 7.05 (s, 1H), 7.25 (d, 1H), 7.50 (s, 1H), 7.53 (d, 1H), 7.58 (s, 1H), 12.50 (bs, 1H).
71		2a	405	403	¹ H NMR δ (d ₆ -DMSO): 1.14 (d, 6H), 1.3-1.4 (m, 2H), 1.42-1.62 (m, 4H), 1.65-1.82 (m, 2H), 3.9 (d, 2H), 4.62-4.78 (m, 1H), 6.68 (s, 1H), 7.22 (s, 2H), 8.12 (s, 1H).

208
707

Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
72		2a	381	379	¹ H NMR δ (d ₆ -DMSO): 1.25 (d, 6H), 3.3 (s, 3H), 3.7 (t, 2H), 4.15 (t, 2H), 4.6-4.8 (hept, 1H), 6.75 (t, 1H), 7.25 (d, 2H), 8.15 (s, 1H), 13.0 (bs, 2H).
73		2a	379	377	¹ H NMR δ (d ₆ -DMSO): 3.85 (s, 3H), 5.25 (s, 2H), 6.9 (m, 1H), 7.2-7.35 (m, 3H), 7.4-7.5 (m, 2H), 7.6-7.7 (t of d, 1H), 8.15 (s, 1H), 13.0 (bs, 2H).
74		2a	401		¹ H NMR δ (d ₆ -DMSO): 0.9 (t, 3H), 1.2-1.3 (d, 3H + d, 6H), 1.5-1.75 (m, 2H), 4.45 (hex, 1H), 4.75 (hept, 1H), 6.7 (t, 1H), 7.2 (d, 2H), 8.15 (s, 1H), 13.0 (bs, 2H).
75		22			¹ H NMR δ (d ₆ -DMSO): 1.31 (d, 6H), 4.82 (m, 1H), 7.26 (d, 1H), 7.56 (d, 1H), 7.59 (s, 1H), 7.94 (d, 1H), 8.15 (s, 1H), 10.00 (s, 1H), 12.77 (bs, 1H).
76		2a			¹ H NMR δ (d ₆ -DMSO): 0.97 (d, 3H), 1.26 (s, 6H), 1.72 (t, 2H), 3.85-4.20 (m, 2H), 4.56-4.83 (m, 1H), 6.69 (s, 1H), 7.00 (s, 1H), 7.26 (s, 1H), 8.11 (s, 1H).
77		2a	359		¹ H NMR δ (d ₆ -DMSO): 1.30 (d, 6H), 3.30 (s, 1H), 4.74 (m, 1H), 4.88 (s, 2H), 6.80 (s, 1H), 7.31 app d, 2H), 8.15 (s, 1H), 10.01 (bs, 1H).
78		2a	407	405	¹ H NMR δ (d ₆ -DMSO): 0.91 (t, 6H), 1.29 (d, 6H), 1.37-1.53 (m, 4H), 1.56-1.70 (m, 1H), 3.30 (d, 2H), 4.73 (m, 1H), 6.72 (s, 1H), 7.26 (app d, 2H), 8.14 (s, 1H), 13.00 (bs, 1H).

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212

Ejemplo	Estructura	Ruta	ME-HL	ME-HL	NMR
79		1	378		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.28 (d, 6H), 2.02 (m, 1H), 3.80 (d, 2H), 4.65 (m, 1H), 6.75 (ap t, 1H), 7.25 (ap d, 2H), 8.68 (s, 1H)
80		28	533		¹ H NMR δ (d ₆ -DMSO): 1.22 (d, 6H), 1.61 (s, 6H), 4.58-4.64 (m, 1H), 6.62 (s, 1H), 7.19 (s, 1H), 7.40 (s, 1H), 8.05 (s, 1H), 8.12 (s, 1H).
81		2a			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 6H), 4.50 (m, 2H), 4.71 (m, 1H), 5.26 (bs, 1H), 7.08 (s, 1H), 7.53 (s, 1H), 7.60 (s, 1H), 8.01 (s, 1H), 13.00 (bs, 1H).
82		21			¹ H NMR δ (d ₆ -DMSO): 1.32 (d, 6H), 2.80 (s, 3H), 3.37-3.63 (m, 4H), 3.95-4.10 (m, 4H), 4.39 (m, 2H), 4.76 (m, 1H), 7.29 (d, 1H), 7.53 (m, 3H), 7.68 (s, 1H), 7.79 (s, 1H), 12.77 (bs, 1H).
83		21			¹ H NMR δ (d ₆ -DMSO): 1.31 (d, 6H), 2.71 (s, 6H), 4.26 (m, 2H), 4.76 (m, 1H), 7.29 (d, 1H), 7.42 (m, 1H), 7.55 (d, 1H), 7.70 (s, 1H), 10.66 (bs, 1H).
84		21			¹ H NMR δ (d ₆ -DMSO): 1.31 (d, 6H), 3.03-3.16 (m, 4H), 3.71-3.95 (m, 4H), 4.34 (m, 2H), 4.77 (m, 1H), 7.47 (m, 1H), 7.72 (m, 2H), 8.13 (s, 1H).
85		21			¹ H NMR δ (d ₆ -DMSO): 0.41 (m, 2H), 0.60 (m, 2H), 1.14 (m, 1H), 1.35 (d, 6H), 2.85 (m, 2H), 4.19 (m, 2H), 4.81 (m, 1H), 7.32 (d, 1H), 7.46

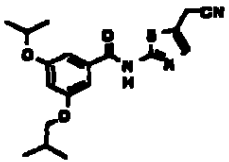
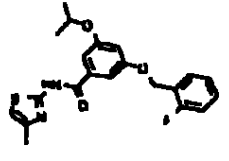
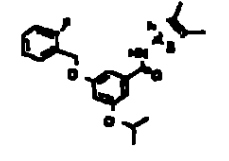
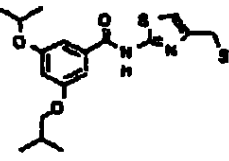
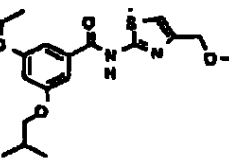
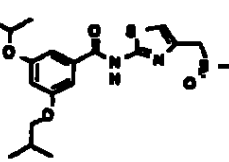
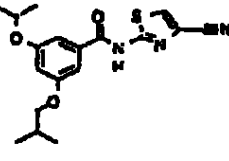
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Ejemplo	Estructura	Ruta	(m/e)	(m/e)	NMR
					(s, 1H), 7.60 (d, 1H), 7.72 (s, 1H), 7.80 (s, 1H), 9.35 (bs, 2H).
86		21			¹ H NMR δ (d ₆ -DMSO): 1.27 (m, 12H), 3.26 (m, 2H), 4.14 (m, 2H), 4.76 (m, 1H), 7.26 (d, 1H), 7.45 (s, 1H), 7.55 (d, 1H), 7.68 (s, 1H), 7.76 (s, 1H), 9.18 (bs, 2H).
87		21			¹ H NMR δ (d ₆ -DMSO): 0.72 (m, 2H), 0.89 (m, 2H), 1.32 (d, 6H), 2.66 (m, 1H), 4.21 (m, 2H), 4.75 (m, 1H), 7.26 (d, 1H), 7.42 (s, 1H), 7.55 (d, 1H), 7.68 (s, 1H), 7.76 (s, 1H);, 9.53 (bs, 2H).
88		1 (See Ex 26)	351	349	¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 3.70 (s, 3H), 4.71 (m, 1H), 4.86 (s, 2H), 6.99 (t, 1H), 7.23 (t, 1H), 7.26-7.27 (m, 2H), 12.53 (s, 1H)
89		24			¹ H NMR δ (d ₆ -DMSO): 1.32 (d, 6H), 4.79 (m, 1H), 7.62 (m, 1H), 7.92 (m, 1H), 8.13 (s, 1H), 8.18 (s, 1H), 10.03 (s, 1H).
90		26	419	417	¹ H NMR δ (d ₆ -DMSO): 1.28 (d, 6H), 2.18 (s, 3H), 2.24 (m, 2H), 2.32 (m, 2H), 3.44 (ap t, 4H), 4.65 (m, 1H), 4.85 (s, 2H), 6.68 (ap t, 1H), 7.19 (m, 1H), 7.24 (ap d, 2H), 7.55 (ap d, 1H), 12.45 (bs, 1H)
91		25			¹ H NMR δ (d ₆ -DMSO): 1.01 (d, 6H), 1.29 (d, 6H), 2.81 (m, 1H), 4.72 (m, 1H), 6.53 (dd, 1H), 6.29 (d, 1H), 6.97 (s, 1H), 7.50 (s, 1H), 7.53 (s, 1H), 8.11 (s, 1H), 8.18 (s, 1H).

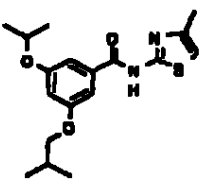
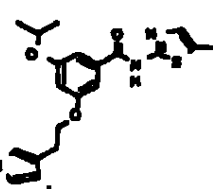
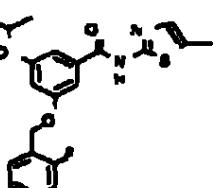
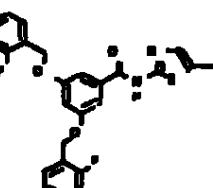
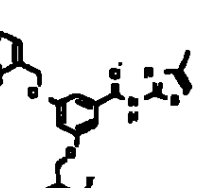
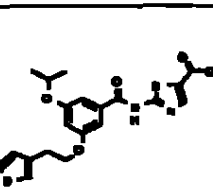
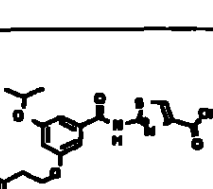
211

Ejemplo	Estructura	Ruta	ME-H	ME-H	NMR
92		1			¹ H NMR δ (d ₆ -DMSO): 1.29 (d, 9H), 4.28 (q, 2H), 4.53 (d, 2H), 4.71 (m, 1H), 5.26 (t, 1H (-OH)), 7.10 (s, 1H), 7.53 (s, 1H), 7.60 (s, 1H), 8.20 (s, 1H), 13.01 (bs, 1H).
93		1			¹ H NMR δ (d ₆ -DMSO): 1.34 (d, 3H), 1.39 (m, 6H), 4.30 (q, 2H), 4.84 (m, 1H), 7.58 (s, 1H), 7.97 (s, 1H), 8.17 (s, 1H), 8.26 (s, 1H), 10.09 (s, 1H).
94		1a	307		
95		1a	307		
96		2aa, 1c	389	387	δ _H (300MHz, DMSO-d ₆) -0.04-0.06 (4H, m); 0.22-0.35 (4H, m); 0.85-1.05 (2H, m); 3.54-4.64 (4H, d); 6.44 (1H, m); 6.93 (6.93-6.97 (2H, m); 7.84 (1H, s)
97		1b (HA TU)	389. 38	387. 34	δ _H (300MHz, DMSO-d ₆) 1.30 (6H, d), 3.08 (2H, t), 4.25 (2H, t), 4.73 (1H, hept), 6.70 (1H, s), 7.14 (1H, d), 7.3 (4H, m), 7.48 (1H, m), 7.57 (1H, d), 12.55 (1H, br s).
98		1a	349		
99		1b (HA	374. 43	372. 39	δ _H (300MHz, DMSO-d ₆) 0.98 (6H, d), 1.27 (6H, d), 2.00 (1H, m), 3.80

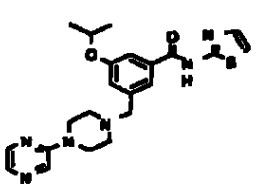
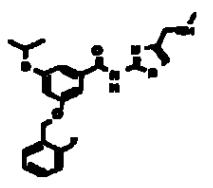
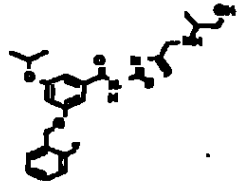
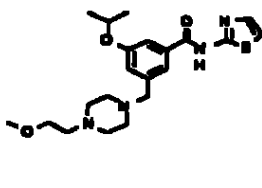
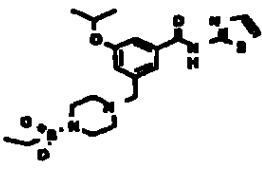
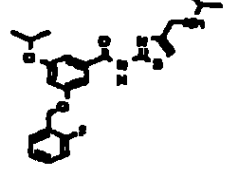
21312

Ejemplo	Estructura	Ruta	(M+H) ⁺	(M+H) ⁺	NMR
		TU)			(2H, d), 4.24 (2H, s), 4.70 (1H, hept), 6.66 (1H, t), 7.23 (2H, d), 7.46 (1H, s), 12.59 (1H, br s).
100		1a	401		
101		1a	415		
102		3 (e) (CM 1a)	395. 19	393. 19	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.35 (6H, d), 2.08 (4H, m), 3.74 (4H, m), 4.60 (1H, hept), 6.64 (1H, m), 6.78 (1H, s), 7.00 (1H, m).
103		3 (e) (CM 1a)	393. 22	391. 21	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.26 (3H, t), 1.35 (6H, d), 2.08 (1H, m), 3.60 (2H, q), 3.74 (d, 2H), 4.47 (2H, s), 4.58 (1H, hept), 6.64 (1H, m), 6.88 (1H, s), 7.02 (1H, m).
104			411. 42	409. 38	δ_H (300MHz, DMSO-d ₆) 0.98 (6H, d), 1.27 (6H, d), 2.02 (1H, m), 2.55 (3H, s), 3.80 (2H, d), 4.14 (2H, s), 4.70 (1H, hept), 6.66 (1H, s), 7.23 (3H, m), 12.62 (1H, br s).
105		1a	427. 39	425. 38	δ_H (300MHz, CDCl ₃) 1.02 (6H, d), 1.36 (6H, d), 2.08 (1H, m), 3.75 (2H, d), 4.60 (1H, hept), 6.68 (1H, m), 7.00 (2H, m), 7.69 (1H, s).

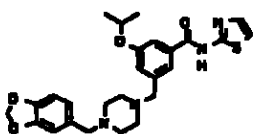
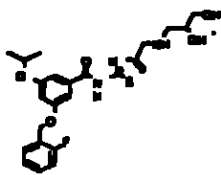
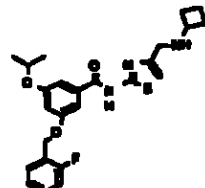
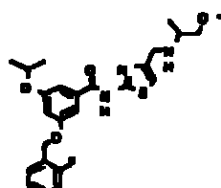
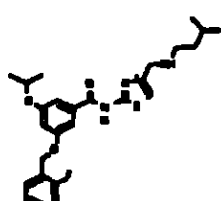
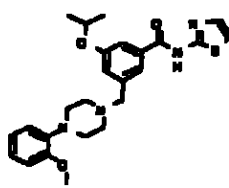
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Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
106		1b (HA TU)	349. 45	347. 43	δ_H (300MHz, CDCl ₃) 0.95 (6H, d), 1.25 (6H, d), 1.95-2.05 (1H, m), 2.2 (3H, s), 3.65 (2H, d), 6.7 (1H, m), 6.98 (1H, m), 7.02 (1H, m).
107		1b (HA TU)	403. 39	401. 37	δ_H (300MHz, DMSO-d ₆) 1.25 (6H, d), 2.38 (3H, s), 3.05 (2H, t), 4.6-4.8 (1H, m), 7.05 (1H, d), 7.10-7.12 (3H, m), 7.15, (1H, m), 7.42-7.45 (1H, m)
108		1b (HA TU)	401. 42	399. 39	δ_H (300MHz, CDCl ₃) 1.25 (6H, d) 2.3 (3H, s), 4.4-4.6 (1H, m) 5.05 (2H, s), 6.65 (1H, m), 6.85 (1H, s), 7.0-7.15 (4H, m) 7.2-7.3 (1H, m), 7.38-7.42 (1H, m).
109		1b (HA TU)	467. 38	465. 37	δ_H (300MHz, DMSO-d ₆) 2.35 (3H, s), 5.2 (4H, s), 6.95 (1H, s), 7.2-7.3 (5H, m), 7.4-7.45 (4H, m), 7.5-7.6 (2H, m).
110		1b (HA TU)	467. 37	465. 38	δ_H (300MHz, CDCl ₃) 1.9 (3H, s), 4.95 (4H, s), 6.4 (1H, s), 6.9-7.1 (6H, m), 7.15-7.25 (2H, m), 7.3-7.4 (2H, m).
111		2a, 1a	433	431	δ_H (500MHz, DMSO-d ₆) 1.27 (6H, d), 3.06 (2H, t), 4.25 (2H, t), 4.72 (1H, m), 6.71 (1H, s), 7.12 (1H, d), 7.23-7.32 (3H, br m), 7.46 (1H, m), 8.10 (1H, s).
112		2a, 1a	433	431	δ_H (500MHz, DMSO-d ₆) 1.28 (6H, d), 3.06 (2H, t), 4.24 (2H, t), 4.72 (1H, m), 6.69 (1H, s), 7.12 (1H, d), 7.27 (1H, s), 7.31 (2H, s), 7.47 (1H, m), 8.02 (1H, s).

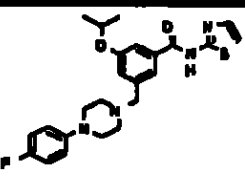
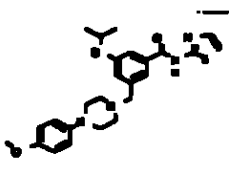
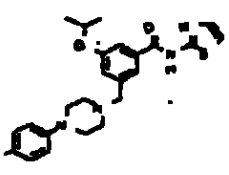
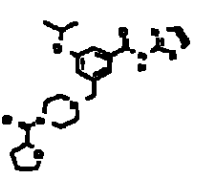
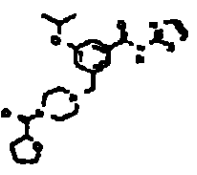
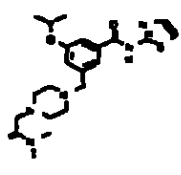
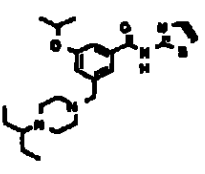
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Ejemplo	Estructura	Ruta	(M.H.)	(M.H.)	NMR
113		21	439. 44	437. 39	δ_H (300MHz, DMSO- d_6) 1.25 (6H, d), 3.0-3.2 (2H, m), 3.3-3.55 (4H, m), 4.3-4.5 (4H, m), 4.75-4.85 (1H, m), 7.25 (1H, d), 7.55-7.6 (2H, m), 7.65 (1H, s), 7.75 (1H, s), 7.95 (1H, s), 8.1 (1H, s), 8.4 (1H, s).
114		3	430. 40	428. 38	δ_H (300MHz, $CDCl_3$) 1.25 (6H, d), 2.42 (3H, s), 3.82 (2H, s), 4.45-4.6 (1H, m), 5.05 (2H, s), 6.6 (1H, s), 6.95-7.15 (3H, m), 7.2-7.25 (2H, m), 7.35-7.45 (1H, m).
115		3	471. 42	472. 40	
116		21	419. 47	417. 44	δ_H (300MHz, DMSO- d_6) 1.25 (6H, d), 3.25 (3H, s), 3.3-3.75 (12H, m), 4.3-4.45 (2H, m), 4.75-4.8 (1H, m), 7.25 (1H, d), 7.5-7.6 (2H, m), 7.7 (1H, s), 7.8 (1H, s).
117		21	453. 39	451. 37	
118		3	458. 39	456. 42	

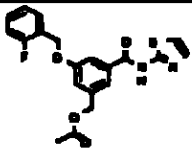
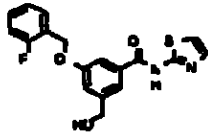
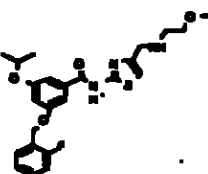
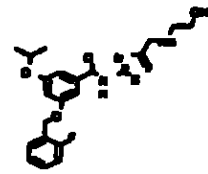
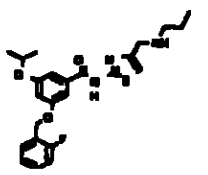
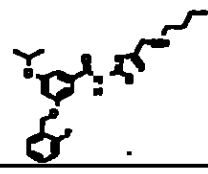
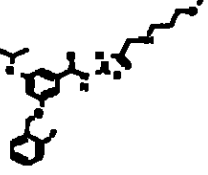
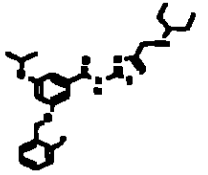
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Ejemplo	Estructura	Ruta	MI-H ₁	MI-H ₂	NMR
119		21	495. 43		δ_H (300MHz, DMSO- d_6) 1.25 (6H, d), 3.3-3.65 (8H, m), 4.2-4.5 (2H, m), 4.7-4.8 (1H, m), 6.05 (2H, s), 6.95 (1H, d), 7.05 (1H, d), 7.25 (2H, m), 7.55 (2H, m), 7.7 (1H, s), 7.8 (1H, s).
120		3	490. 43	488. 42	
121		3	470. 48	468. 47	
122		3	488. 49	486. 47	
123		3	486. 51	484. 51	
124		21	467. 50	465. 49	
125		21	455. 48		

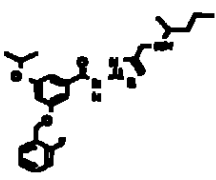
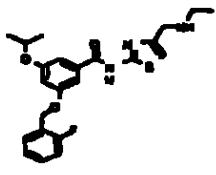
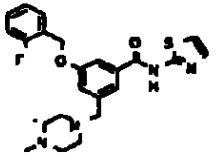
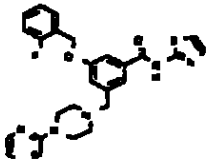
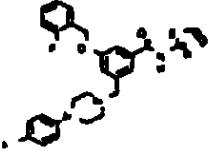
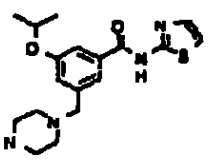
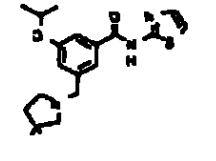
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Ejemplo	Estructura	Ruta	MS-16	MS-16	NMR
			453. 46		
126		21	467. 50	465. 48	
127		21	453. 49	451. 47	
128		21	459. 49	457. 47	
129		21	390. 51	388. 47	
130		21	446. 51	444. 49	
131		21	431. 55	429. 51	
132		1b (HA TU)	401. 35	399. 33	δ_H (300MHz, DMSO- d_6) 2.08 (3H, s), 5.12 (2H, s), 5.24 (2H, s), 7.23 (4H, m), 7.42 (1H, m),

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Ejemplo	Estructura	Ruta	AM (H)	AM (H)	NMR
					7.56 (2H, m), 7.68 (1H, s), 7.76 (1H, s), 12.64 (1H, br s).
133		2a (f)	459.43	357.39	δ_H (300MHz, DMSO- d_6) 4.55 (2H, d), 5.23 (2H, s), 7.23 (4H, m), 7.42 (1H, m), 7.56 (2H, m), 7.68 (2H, m), 12.56 (1H, br s).
134		3	474.48	472.47	
135		3	460.46	548.43	
136		3	458.48	456.47	
137		3	472.51	470.49	
138		3	488.51	486.52	
139		3	486.49	484.47	
140		3	486.	484.	

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Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
			50	49	
141		3	444. 45	442. 41	
142		21	441. 43	439. 42	δ_H (300MHz, DMSO- d_6) 2.82 (3H, s), 3.49 (8H, m), 4.54 (1H, d), 5.24 (3H, m), 7.30 (3H, m), 7.45 (2H, m), 7.59 (2H, m), 7.81 (2H, m), 12.65 (1H, br s).
143		21	505. 45	503. 38	δ_H (300MHz, DMSO- d_6) 3.15 (2H, m), 3.45 (2H, m), 4.25 (4H, m), 4.52 (1H, d), 5.25 (3H, m), 7.27 (3H, m), 7.45 (1H, m), 7.62 (3H, m), 7.90 (3H, m), 8.16 (1H, s), 8.42 (1H, s), 12.70 (1H, br s).
144		21	521. 43		δ_H (300MHz, DMSO- d_6) 3.33 (8H, m), 4.52 (1H, d), 5.27 (3H, m), 7.03 (5H, m), 7.28 (3H, m), 7.45 (1H, m), 7.65 (3H, m), 7.89 (1H, m), 9.20 (1H, br s), 12.69 (1H, br s).
145		21	361. 50	359. 46	δ_H (300MHz, $CDCl_3$) 1.36 (6H, d), 2.56 (4H, m), 3.04 (4H, m), 3.53 (2H, s), 4.61 (1H, hept), 6.95 (1H, d), 7.07 (1H, m), 7.24 (1H, m), 7.44 (2H, m).
146		21	382. 12	380. 13	^1H NMR δ ($CDCl_3$): 1.37 (d, 6H), 2.3 (m, 2H), 2.7 (m, 2H), 2.7 (m, 2H), 2.85 (m, 2H), 4.6 (m, 1H), 6.95 (m, 1H), 7.1 (m, 1H), 7.2 (m, 1H).

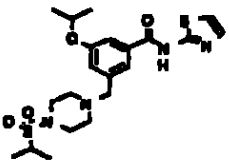
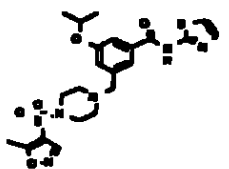
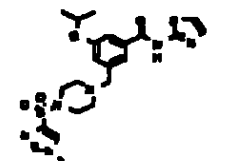
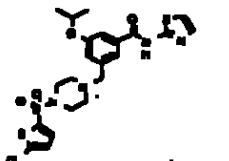
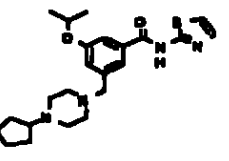
219
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Ejemplo	Estructura	Ruta	AMU	AMU	NMR
					7.4 (m, 2H)
147		21	396.45	394.4	¹ H NMR δ (CDCl ₃): 1.37 (d, 6H), 1.95 (m, 4H), 2.5 (m, 4H), 3.55 (s, 2H), 4.6 (m, 1H), 7.0 (d, 1H), 7.1 (m, 1H), 7.6 (m, 1H)
148		1b (HA TU)	382.12	380.13	¹ H NMR δ (CDCl ₃): 1.37 (d, 6H), 2.3 (m, 2H), 2.7 (m, 2H), 2.7 (m, 2H), 2.85 (m, 2H), 4.6 (m, 1H), 6.95 (m, 1H), 7.1 (m, 1H), 7.2 (m, 1H), 7.4 (m, 2H)
149		1b (HA TU)	403.39	401.36	δ _H (300MHz, DMSO-d ₆) 2.09 (3H, s), 3.26 (2H, t), 4.30 (2H, t), 5.08 (2H, s), 6.98 (2H, m), 7.17 (1H, s), 7.26 (1H, d), 7.35 (1H, m), 7.54 (1H, d), 7.64 (2H, br s), 12.62 (1H, br s).
150		2a (g)	361.41	359.38	
151		3	432.40	430.37	
152		3	476.48	474.47	
153		3	472.48	470.45	
154		3	462.45	460.43	

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Ejemplo	Estructura	Ruta	MS (M ⁺)	MS (M ⁺)	NMR
155		21	462. 41	460. 38	
156		21	521. 42	519. 40	
157		21	507. 48		
158		21	453. 52	451. 49	¹ H NMR δ (CDCl ₃): 1.35 (d, 6H), 2.5 (m, 2H), 3.65 (m, 4H), 4.65 (m, 1H), 6.3 (d, 1H), 6.95 (d, 1H), 7.1 (m, 1H), 7.35 (d, 1H), 7.5 (m, 1H), 7.58 (s, 1H), 8.1 (d, 1H)
159		21	461. 49	459. 48	
160		1b (HA TU) (h)	453. 44	451. 40	
161		1b (HA TU) (h)	406. 40		
162		21 (i)	467.	465.	

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Ejemplo	Estructura	Ruta	ME (g)	ME (g)	NMR
			50	49	
163		21 (i)	506.47	504.46	
164		21 (i)	505.46	503.43	
165		21 (i)	541.39	539.35	
166		21	429.54	427.51	

Notas:

* Productos finales preparados por el método de hidrólisis 2a; materiales iniciales requeridos preparados de acuerdo con la metodología genérica de alquilación seguida por acoplamiento (Ruta 1).

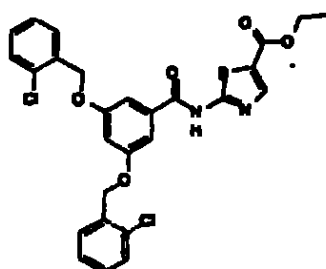
** Productos finales preparados por el método de aminación reductora 6; materiales iniciales requeridos preparados de acuerdo con la metodología genérica de alquilación seguida por acoplamiento (Ruta 1) e hidrólisis (Ruta 2a).

*** Productos finales preparados por hidrólisis (Ruta 2a) o acoplamiento de

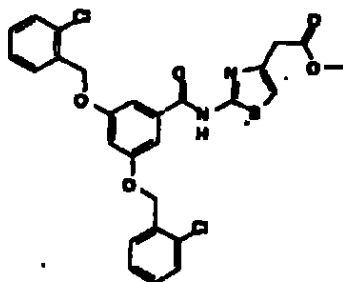
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222
222

cloruro de ácido (Ruta 1); materiales iniciales requeridos preparados de acuerdo con la metodología genérica de alquilación seguida por acoplamiento (Ruta 1).

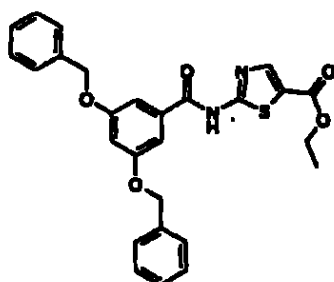
**** Para los Ejemplos II₂, II₇, II₈, II₁₅ y II₂₆ los intermedios éster se prepararon por ruta 1:



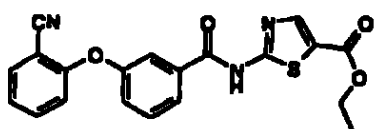
¹H NMR δ (d₆-DMSO): 1.3 (3H, t); 4.3 (2H, q); 5.25 (4H, s); 7.0 (1H, t); 7.4 (6H, m); 7.5 (2H, m); 7.6 (2H, m); 8.2 (1H, s).



ejemplificado como Ejemplo II₃

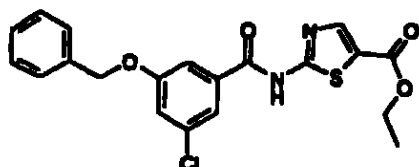


¹H NMR δ (d₆-DMSO): 1.3 (3H, t); 4.3 (2H, q); 5.2 (4H, s); 6.95 (1H, t); 7.2-7.5 (12H, m); 8.2 (1H, s); 13.05 (1H, br s); el espectro contiene también señales debido a cantidades trazadoras de 2-aminotiazol.



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no caracterizado.



MH⁺ = 389, 391

M-H = 387, 389

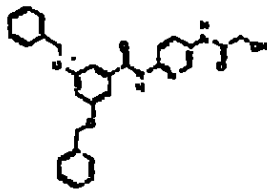
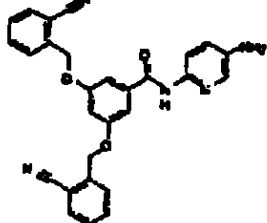
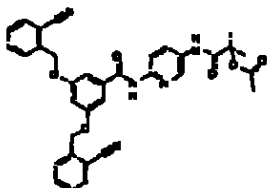
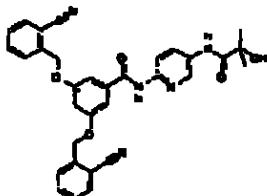
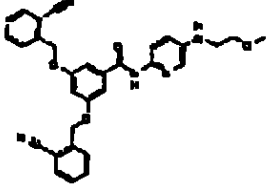
EJEMPLO JJ:

Por métodos análogos a los descritos más arriba se prepararon también los siguientes compuestos, Ejemplos número JJ₁ a JJ₃₇.

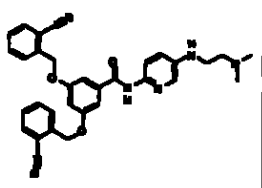
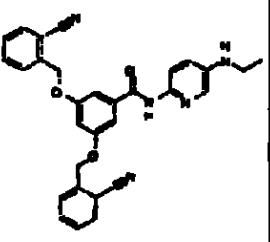
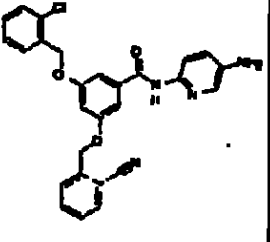
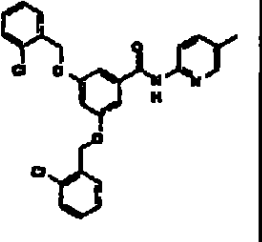
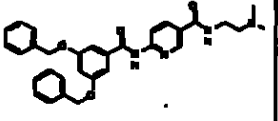
Ejemplo	Estructura	Ruta	ΔH ₁ -H ₂	ΔH ₂ -H ₃	NMR
1		7	426.19	424.25	¹ H NMR d (d6-DMSO): 5.17 (m, 6H), 6.80 (s, 1H), 7.00 (d, 1H), 7.26 a 7.46 (m, 12H), 7.71 (s, 1H), 7.78 (d, 1H), 10.28 (brs, 1H)
2		8		552.22	¹ H NMR d (d6-DMSO): 1.55 (s, 6H), 2.08 (s, 3H), 5.18 (s, 4H), 6.85 (s, 1H), 7.29 a 7.50 (m, 12H), 7.98 (dd, 1H), 8.13 (d, 1H), 8.61 (s, 1H), 9.70 (s, 1H), 10.72 (s, 1H)
3		9	512.16	510.22	¹ H NMR d (d6-DMSO): 1.35 (s, 6H), 5.18 (s, 4H), 6.88 (s, 1H), 7.28 a 7.48 (m, 12H), 8.08 (d, 1H), 8.22 (d, 1H), 8.82 (s, 1H), 9.90 (s, 1H), 10.96 (s, 1H)
4		8		502.49	¹ H NMR d (d6-DMSO): 3.02 (s, 3H), 5.17 (s, 4H), 6.86 (s, 1H), 7.29 a 7.58 (m, 12H), 7.70 (d, 1H), 8.13 (d, 1H), 8.24 (s, 1H), 9.83 (s, 1H), 10.83

Ejemplo	Estructura	Ruta	(M.H.)	(M.H.)	NMR (s, 1H)
5		8	526.41	524.45	1H NMR d (d6-DMSO): 2.13 (s, 3H), 4.65 (s, 2H), 5.18 (s, 4H), 6.84 (s, 1H), 7.27 a 7.48 (m, 12H), 7.96 (d, 1H), 8.13 (d, 1H), 8.61 (s, 1H), 10.24 (s, 1H), 10.73 (s, 1H)
6		8	498.55	496.55	1H NMR d (d6-DMSO): 3.39 (s, 3H), 4.01 (s, 1H), 5.18, (s, 4H), 6.85 (s, 1H), 7.28 a 7.50 (m, 12H), 8.07 (m, 2H), 8.67 (s, 1H), 9.95 (s, 1H), 10.71 (s, 1H)
7		8	540.58	539.63	1H NMR d (d6-DMSO): 1.20 (t, 3H), 3.47 (s, 2H), 4.11 (q, 2H), 5.17 (s, 4H), 6.83 (s, 1H), 7.28 a 7.48 (m, 12H), 7.95 (d, 1H), 8.13 (d, 1H), 8.60 (s, 1H), 10.35 (s, 1H), 10.73 (s, 1H)
8		8	526.53	524.61	1H NMR d (d6-DMSO): 1.30 (t, 3H), 4.30 (q, 2H), 5.17 (s, 4H), 6.86 (s, 1H), 7.28 a 7.50 (m, 12H), 8.14 (s, 2H), 8.74 (s, 1H), 10.78 (s, 1H), 10.97 (s, 1H)
9		10	525.61	523.66	1H NMR d (d6-DMSO): 1.30 (s, 9H), 5.18 (s, 4H), 6.09 (s, 1H), 6.85 (s, 1H), 7.32-7.50 (m, 12H), 7.78 (dd, 1H), 8.04 (d; 1H), 8.38 (s, 1H), 8.44 (s, 1H), 10.65 (s, 1H)
10		9	512.4		1H NMR d (d6-DMSO): 3.41 (s, 2H), 5.17 (s, 4H), 6.90 (s, 1H), 7.29 a 7.54 (m, 12H), 8.03 (d, 1H), 8.13 (d, 1H), 8.70 (s,

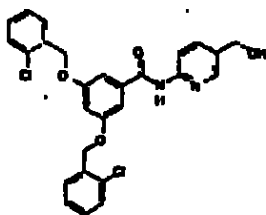
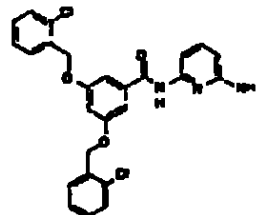
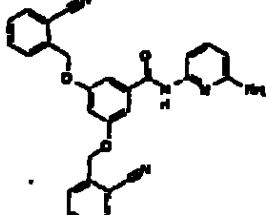
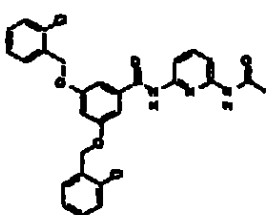
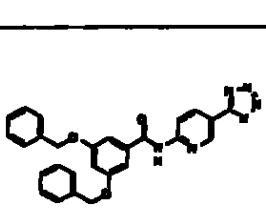
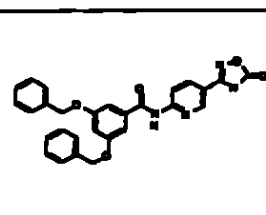
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Ejemplo	Estructura	Ruta	Δ MF (H)	Δ MF (C)	NMR
					1H), 10.50 (s, 1H), 10.85 (s, 1H)
11		9	484.4		1H NMR d (d6-DMSO): 4.04 (s, 2H), 5.20 (s, 4H), 6.89 (s, 1H), 7.30 a 7.51 (m, 12 H), 8.12 (d, 1H), 8.22 (d, 1H), 8.81 (s, 1H), 10.05 (s, 1H), 11.00 (s, 1H)
12		7	476.36		1H NMR d (d6-DMSO): 5.14 (s, 2H), 5.32 (s, 4H), 6.90 (s, 1H), 7.01 (dd, 1H), 7.35 (s, 2H), 7.59 (m, 2H), 7.80 (m, 6H), 7.90 (d, 2H), 10.38 (s, 1H) + 0.1 EtOAc
13		8	604.29	602.3	1H NMR d (d6-DMSO): 1.55 (s, 6H), 2.07 (s, 3H), 5.33 (s, 4H), 6.95 (s, 1H), 7.40 (s, 2H), 7.56 (m, 2H), 7.73 (m, 4H), 7.90 (d, 2H), 7.98 (dd, 1H), 8.13 (d, 1H), 8.63 (s, 1H), 9.71 (s, 1H), 10.82 (s, 1H)
14		9	562.28	560.27	1H NMR d (d6-DMSO): 1.34 (s, 6H), 5.32 (s, 4H), 6.97 (s, 1H), 7.40 (s, 2H), 7.57 (m, 2H), 7.75 (m, 4H), 7.90 (d, 2H), 8.09 (d, 1H), 8.21 (dd, 1H), 8.82 (s, 1H), 9.90 (s, 1H), 10.99 (s, 1H)
15		11	534.41		1H NMR d (d6-DMSO): 3.22 (t, 2H), 3.28 (t, 3H), 3.50 (t, 2H), 5.31 (s, 4H), 6.92 (s, 1H), 7.12 (dd, 1H), 7.34 (s, 2H), 7.57 (m, 2H), 7.75 (m, 5H), 7.82 (d, 1H), 7.91 (d, 2H), 10.49 (brs, 1H)
16		11	547.86		1H NMR d (d6-DMSO): 2.20 (s, 6H),

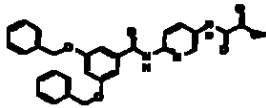
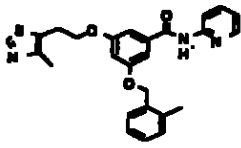
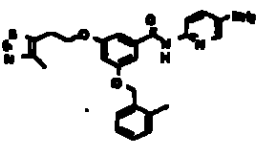
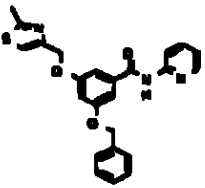
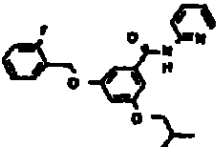
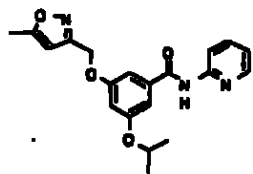
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Ejemplo	Estructura	Ruta	λ_{max}	λ_{min}	NMR
					^1H NMR d (3.12 (m, 2H), 5.32 (s, 4H), 5.51 (br s, 1H), 6.89 (s, 1H), 7.06 (dd, 1H), 7.37 (s, 2H), 7.57 (m, 2H), 7.74 (m, 5H), 7.83 (d, 1H), 7.92 (d, 2H), 10.41 (s, 1H), and 2H under DMSO o water
17		11	504.54		^1H NMR d (d6-DMSO): 1.15 (t, 3H), 3.06 (quartet, 2H), 5.32 (s, 4H), 6.90 (s, 1H), 7.00 (dd, 1H), 7.35 (s, 2H), 7.57 (m, 2H), 7.73 (m, 5H), 7.85 (d, 1H), 7.92 (d, 2H), 10.41 (s, 1H)
18		12	485.5	483.5	^1H NMR d (d6-DMSO): 5.13 (s, 2H), 5.18 (s, 2H), 5.31 (s, 1H), 6.88 (s, 1H), 7.00 (dd, 1H), 7.32 (s, 2H), 7.40 (m, 3H), 7.50 (s, 1H), 7.58 (m, 1H), 7.74 (m, 3H), 7.80 (d, 1H), 7.90 (d, 1H), 10.33 (s, 1H)
19		1	493, 495		^1H NMR d (d6-DMSO): 2.35 (3H, s); 5.31 (4H, s); 6.98 (1H, t); 7.43-7.48 (6H, m); 7.58-7.61 (2H, m); 7.65-7.71 (3H, m); 8.14 (1H, d); 8.29 (1H, s); 10.84 (1H, s)
20		13	525		^1H NMR d (d6-DMSO): 3.10 (2H, m); 3.30 (6H, s); 3.60 (2H, m); 5.19 (4H, s); 6.89 (1H, s); 7.31-7.48 (12H, m); 8.29 (2H, m); 8.92 (1H, s); 11.05 (1H, s)
21		14	509		^1H NMR d (d6-DMSO): 4.5 (1H, d), 5.25 (s, 4H), 6.9 (s, 1H), 7.40 (m, 6H), 7.5 (m, 2H), 7.6 (m, 2H), 7.75 (dd,

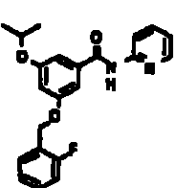
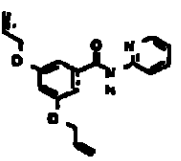
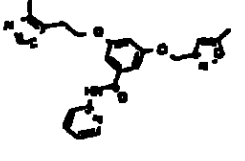
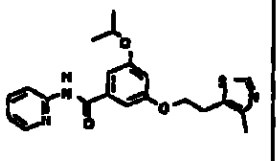
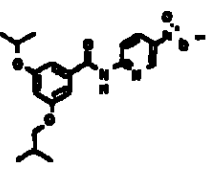
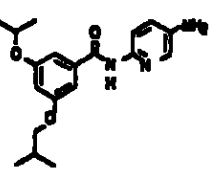
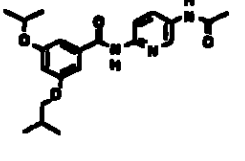
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Ejemplo	Estructura	Ruta	MS-10	MS-11	NMR
					¹ H, 8.10 (d, 1H), 8.3 (s, 1H), 10.8 (br s, 1H);
22		1	494/496		¹ H NMR d (d6-DMSO): 5.25 (4H, s); 5.65 (2H, s); 6.23 (1H, d); 6.85 (1H, s); 7.05-7.15 (3H, m); 7.18-7.22 (5H, m); 7.45-7.55 (2H, m); 7.58-7.62 (2H, m); 10.16 (1H, br s).
23		1	476		¹ H NMR d (d6-DMSO): 5.25 (4H, s); 5.75 (2H, s); 6.22 (1H, d); 6.90 (1H, s); 7.25-7.41 (4H, m); 7.50-7.60 (2H, m); 7.70-7.80 (4H, m); 7.90 (2H, d); 10.19 (1H, br s).
24		15	536/538		¹ H NMR d (d6-DMSO): 3.25 (3H, s); 5.20 (4H, s); 6.9 (1H, t); 7.25 (2H, d); 7.35-7.40 (4H, m); 7.4-7.55 (2H, m); 7.58-7.63 (2H, m); 7.68-7.72 (1H, m); 7.75-7.80 (2H, d); 10.14 (1H, br s); 10.36 (1H, br s).
25		16	479	477	¹ H NMR d (d6-DMSO): 5.19 (4H, s); 6.88 (1H, s); 7.26-7.48 (12H, m); 8.40 (1H, d); 8.46 (1H, dd); 9.04 (1H, s); 11.13 (1H, br s).
26		17	495	493	¹ H NMR d (d6-DMSO): 5.19 (4H, s); 6.87 (1H, s); 7.28-7.46 (12H, m); 8.21 (1H, dd); 8.38 (1 H, d); 8.79 (1H, s); 11.14 (1H, br s).
27		18	498		¹ H NMR d (d6-

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Ejemplo	Estructura	Ruta	ME II	ME III	NMR
					DMSO): 5.18 (4H, s); 6.88 (1H, s); 7.30-7.50 (12H, m); 8.17 (2H, s); 8.79 (1H, s); 10.79 (1H, s); 10.93 (1H, br s).
28		1	460		¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.36 (s, 3H), 3.23 (t, 2H), 4.22 (t, 2H), 5.13 (s, 2H), 6.78 (m, 1H), 7.11-7.24 (brm, 5H), 7.30 (m, 1H), 7.41 (d, 1H), 7.83 (m, 1H), 8.14 (d, 1H), 8.37 (m, 1H), 8.82 (s, 1H), 10.74 (brs, 1H)
29		7	475		¹ H NMR δ (d ₆ -DMSO): 2.32 (s, 3H), 2.36 (s, 3H), 3.22 (t, 2H), 4.20 (t, 2H), 5.11 (s, 4H), 6.72 (m, 1H), 7.00 (m, 1H), 7.15-7.28 (brm, 5H), 7.41 (d, 1H), 7.73 (m, 2H), 8.82 (s, 1H), 10.29 (brs, 1H).
30		1			¹ H NMR δ (d ₆ -DMSO): 2.66 (s, 3H), 5.15 (s, 4H), 6.88 (m, 1H), 7.14 (m, 1H), 7.39-7.47 (brm, 7H), 7.52 (s, 1H), 7.83 (m, 1H), 8.15 (d, 1H), 8.38 (m, 1H), 10.72 (brs, 1H).
31		1b	395		
32		1			¹ H NMR δ (d ₆ -DMSO): 1.28 (d, 6H), 2.39 (s, 3H), 4.72 (m, 1H), 5.20 (s, 2H), 6.33 (s, 1H), 6.72 (s, 1H), 7.14 (m, 1H), 7.20 (s, 1H), 7.27 (s, 1H), 7.82 (m, 1H), 8.13 (d, 1H), 8.36 (d, 1H), 10.72 (brs, 1H).

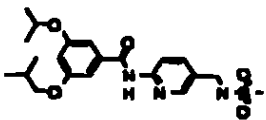
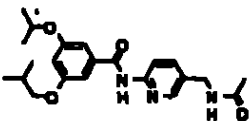
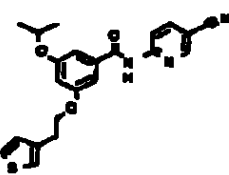
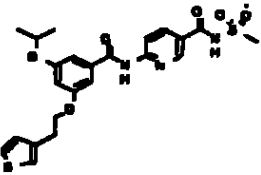
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D

Ejemplo	Estructura	Ruta	MI-H ₂	MI-H ₂	NMR
33		1			¹ H NMR δ (d ₆ -DMSO): 1.27 (d, 6H), 4.71 (m, 1H), 5.21 (s, 2H), 6.73 (t, 1H), 7.12-7.29 (brm, 5H), 7.22 (m, 1H), 7.56 (m, 1H), 7.83 (m, 1H), 8.14 (d, 1H), 8.35 (m, 1H), 10.72 (brs, 1H).
34		1b	311		
35		1b	451		
36		1b	398		
37		1	374	372	¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 2.01 (m, 1H), 3.60 (d, 2H), 4.71 (m, 1H), 6.67 (ap t, 1H), 7.17 (ap d, 2H), 8.39 (d, 1H), 8.63 (dd, 1H), 9.20 (d, 1H), 11.43 (bs, 1H)
38		7b	344		¹ H NMR δ (d ₆ -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.00 (m, 1H), 3.78 (d, 2H), 4.69 (m, 1H), 5.12 (s, 2H), 6.58 (t, 1H), 6.99 (dd, 1H), 7.1 (ap d, 2H), 7.73-7.78 (m, 2H), 10.24 (bs, 1H)
39		15	386		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.26 (d, 6H), 2.01 (m, 1H), 2.05 (s, 3H), 3.79 (d, 2H), 4.70 (m, 1H), 6.61 (ap t, 1H), 7.14 (ap d, 2H), 7.95 (dd, 1H), 8.08 (d, 1H), 7.59

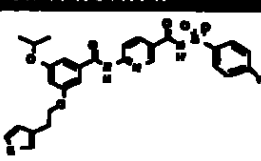
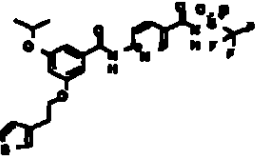
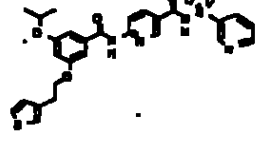
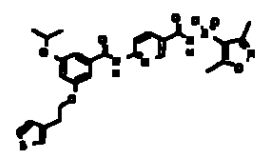
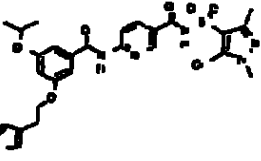
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Ejemplo	Estructura	Ruta	(M+H) ⁺	(M-H) ⁻	NMR
					(ap d, 1H), 10.07 (bs, 1H)
40		15	422	420	¹ H NMR δ (d ₆ -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.03 (m, 1H), 3.01 (s, 3H), 3.79 (d, 2H), 4.70 (m, 1H), 6.63 (ap t, 1H), 7.14 (ap d, 2H), 7.70 (dd, 1H), 8.12 (d, 1H), 8.34 (ap d, 1H), (9.83, s, 1H), 10.81 (bs, 1H)
41		9	M+H 430 M-H 428		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 1.35 (s, 6H), 2.01 (m, 1H), 3.79 (d, 2H), 4.70 (m, 1H), 5.71 (s, 1H), 6.61 (s, 1H), 7.15 (s, 2H), 8.06-8.15 (m, 2H), 8.76 (ap d, 1H), 9.78 (s, 1H), 10.65 (bs, 1H)
42		15	412 (M+H CO OH) ⁺ 456		¹ H NMR δ (d ₆ -DMSO): 0.79-0.82 (m, 4H), 0.98 (d, 6H), 1.26 (d, 6H), 1.77 (m, 1H), 2.01 (m, 1H), 4.70 (h, 1H), 6.11 (ap t, 1H), 7.14 (ap d, 2H), 7.95 (dd, 1H), 8.08 (d, 1H), 8.62 (ap d, 1H), 10.33 (bs, 1H), 10.64 (bs, 1H)
43		27	M+H 450 M-H 448		¹ H NMR δ (d ₆ -DMSO): 0.98 (d, 6H), 1.27 (d, 6H), 2.01 (m, 1H), 3.37 (s, 3H), 3.80 (d, 2H), 4.71 (m, 1H), 6.65 (ap t, 1H), 7.17 (s, 2H), 8.27-8.35 (m, 2H), 8.91 (m, 1H), 11.13 (bs, 1H)
44		1c	352		δ _H (300MHz, DMSO-d ₆) 0.94-1.02 (6H, d); 1.24-1.34 (6H, d); 1.095-2.10 (1H, m); 3.76-3.84 (2H, d); 4.64-4.77 (1H, m); 6.64-6.70 (1H, m); 7.14-7.17 (2H, m); 8.25-8.36 (2H, m); 8.85 (1H, m); 11.21 (1H, s)

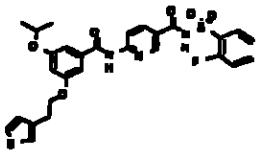
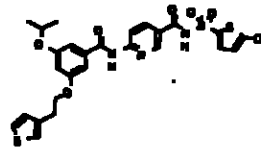
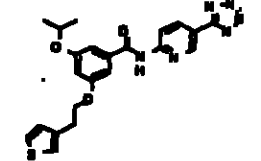
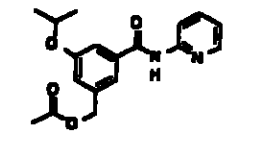
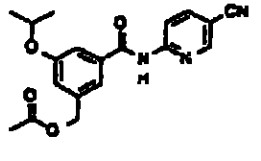
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Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
45		8 (a) 7c			δ_H (300MHz, DMSO- d_6) 0.94-1.03 (6H, d); 1.26-1.30 (6H, d); 1.95-2.08 (1H, m); 2.90 (3H, s); 3.75-3.84 (2H, d); 4.04-4.26 (2H, d + H ₂ O); 4.65-4.77 (1H, m); 6.64 (1H, m); 7.15 (2H, m); 7.50-7.62 (1H, broad t); 7.80-7.90 (1H, d of m); 8.08-8.16 (1H, app d); 8.35 (1H, m); 10.84 (1H, m)
46		8 (a) 7c			δ_H (300MHz, DMSO- d_6) 0.94-1.02 (6H, d); 1.24-1.30 (6H, d); 1.84 (3H, s); 1.95-2.07 (1H, m); 3.75-3.83 (2H, d); 4.18-4.27 (2H, d); 4.64-4.76 (1H, m); 6.62 (1H, m); 7.15 (2H, m); 7.63-7.73 (1H, app d of m); 8.05-8.13 (1H, app d); 8.27 (1H, s); 8.30-8.38 (1H, app broad t); 10.69 (1H, s)
46a		1a	408	406	δ_H (300MHz, DMSO- d_6) 1.26 (d, 6H), 3.05 (t, 2H), 4.25 (t, 2H), 4.72 (sept, 1H), 6.68 (s, 1H), 7.12 (d, 1H), 7.16 (s, 1H), 7.19 (s, 1H), 7.33 (s, 1H), 7.47 (dd, 1H), 8.30 (m, 2H), 8.83 (s, 1H), 11.23 (bs, 1H)
47		27	504		δ_M (300MHz, DMSO- d_6) 1.27 (d, 6H), 3.06 (t, 2H), 3.38 (s, 3H), 4.25 (t, 2H), 4.71 (sept, 1H), 6.68 (t, 1H), 7.11 (dd, 1H), 7.12 (s, 1H), 7.17 (s, 1H), 7.31 (d, 1H), 7.46 (dd, 1H), 8.29 (d, 1H), 8.34 (dd, 1H), 8.92 (d, 1H), 11.14 (bs, 1H)
48		27	584	582	δ_H (300MHz, DMSO- d_6) 1.25 (d, 6H), 3.04 (t, 2H), 4.23 (t, 2H), 4.69

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Ejemplo	Estructura	Ruta	$\delta_{\text{C}}(^{13}\text{C})$	$\delta_{\text{H}}(^1\text{H})$	NMR
					(sept; 1H), 6.67 (s, 1H), 7.11 (d, 1H), 7.15 (s, 1H), 7.20 (s, 1H), 7.31 (d, 1H), 7.46 (m, 3H), 8.07 (dd, 2H), 8.26 (s, 2H), 8.86 (s, 1H), 11.13 (bs, 1H)
49		27	556		δ_{H} (300MHz, DMSO- d_6) 1.27 (d, 6H), 3.04 (t, 2H), 4.23 (t, 2H), 4.71 (sept, 1H), 6.64 (s, 1H), 7.11 (d, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.32 (s, 1H), 7.46 (dd, 1H), 8.19 (m, 2H), 8.82 (d, 1H), 10.93 (bs, 1H)
50		27	567		δ_{H} (300MHz, DMSO- d_6) 1.26 (d, 6H), 3.04 (t, 2H), 4.24 (t, 2H), 4.70 (sept, 1H), 6.64 (t, 1H), 7.11 (dd, 1H), 7.16 (s, 1H), 7.21 (s, 1H), 7.30 (m, 1H), 7.46 (m, 1H), 8.16 (m, 3H), 8.62 (d, 1H), 8.83 (s, 1H), 8.98 (s, 1H), 10.90 (bs, 1H)
51		27	585	583	δ_{H} (300MHz, DMSO- d_6) 1.27 (d, 6H), 2.39 (s, 3H), 2.68 (s, 3H), 3.06 (t, 2H), 4.26 (t, 2H), 4.73 (sept, 1H), 6.69 (t, 1H), 7.12 (d, 1H), 7.17 (s, 1H), 7.22 (s, 1H), 7.33 (m, 1H), 7.49 (m, 1H), 8.28 (m, 2H), 8.89 (s, 1H), 11.10 (bs, 1H)
52		27	618/620 (1xCl)	616/618 (1xCl)	δ_{H} (300MHz, DMSO- d_6) 1.28 (d, 6H), 2.40 (s, 3H), 3.08 (t, 2H), 3.79 (s, 3H), 4.25 (t, 2H), 4.71 (sept, 1H), 6.68 (s, 1H), 7.12 (d, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.34 (m, 1H), 7.39 (s, 1H), 7.48 (dd, 1H), 8.30 (m, 2H), 8.92 (s, 1H), 11.15 (bs, 1H)

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Ejemplo	Estructura	Ruta	1H-NMR	13C-NMR	NMR
53		27	584		δ_H (300MHz, DMSO- d_6) 1.26 (d, 6H), 3.04 (t, 2H), 4.24 (t, 2H), 4.70 (sept, 1H), 6.66 (t, 1H), 7.12 (dd, 1H), 7.18 (s, 1H), 7.22 (s, 1H), 7.30 (m, 1H), 7.37 (m, 1H), 7.45 (dd, 1H), 7.67 (m, 1H), 7.78 (dt, 1H), 7.96 (dt, 1H), 8.822 (s, 2H), 8.86 (s, 1H), 11.08 (bs, 1H)
54		27	606	604	δ_H (300MHz, DMSO- d_6) 1.26 (d, 6H), 3.04 (t, 2H), 4.25 (t, 2H), 4.71 (sept, 1H), 6.64 (t, 1H), 7.00 (d, 1H), 7.12 (dd, 1H), 7.16 (s, 1H), 7.22 (s, 1H), 7.32 (m, 2H), 7.46 (dd, 1H), 8.14 (d, 1H), 8.22 (dd, 1H), 8.83 (t, 1H), 10.87 (bs, 1H)
55		16	451	449	δ_H (300MHz, DMSO- d_6) 1.28 (d, 6H), 3.06 (t, 2H), 4.26 (t, 2H), 4.72 (sept, 1H), 6.65 (s, 1H), 7.12 (d, 1H), 7.18 (s, 1H), 7.23 (s, 1H), 7.32 (s, 1H), 7.47 (m, 1H), 8.23 (d, 1H), 8.32 (dd, 1H), 8.95 (s, 1H), 10.81 (bs, 1H)
56		1a	329.48	327.46	
57		1a	354.46	352.43	

Notas:

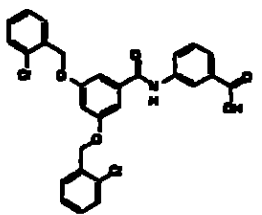
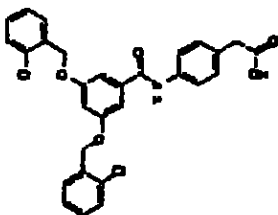
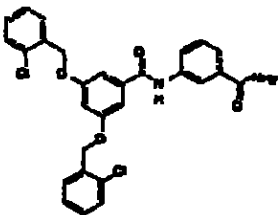
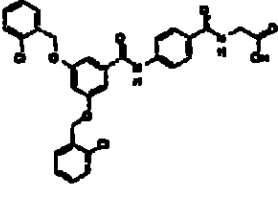
* Productos finales preparados por el método de hidrólisis 2a; materiales

***** Productos finales preparados por hidrólisis (Ruta 2a) o acoplamiento de cloruro de ácido (Ruta 1); materiales iniciales requeridos de acuerdo con la metodología de alquilación genérica seguida por acoplamiento (Ruta 1).**

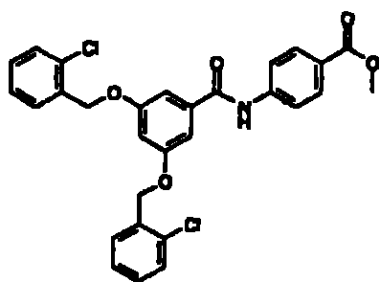
Por métodos análogos a los descritos más arriba se elaboraron también los siguientes compuestos, Ejemplos número KK₁ a KK₇.

Ejemplo	Estructura	Ruta	(XII-III)	(XI-III)	NMR
1		2b *	522	520	¹ H NMR d (d6-DMSO): 5.20 (4H, s); 6.95 (1H, s); 7.25 (2H, s); 7.30-7.5 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 7.8 - 8.0 (4H, s).
2		1	494		Sin datos
3		1		556/ 558	NMR no correcta
4		2b	522		¹ H NMR d (d6-DMSO): 5.25 (4H, s); 6.95 (1H, s); 7.25 (2H, s); 7.35-7.55 (7H, m); 7.6 - 7.7 (3H, m); 8.05 (1H, d); 8.4 (1H, s); 10.3 (1H, br s);

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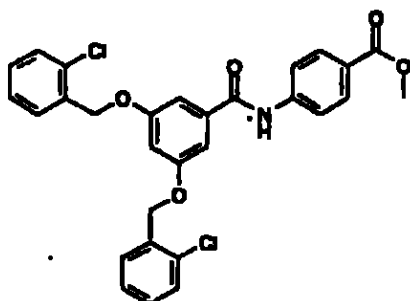
Ejemplo	Estructura	Ruta	(M-H) ⁺	(M-H) ⁻	NMR
					12.9 (1H, br s).
5		2b *	536	534	¹ H NMR d (d6-DMSO): 3.4 (2H, s); 5.2 (4H, s); 6.95 (1H, s); 7.2 (4H, m); 7.4 (4H, m); 7.5 (2H, m); 7.6 -7.7 (4H, m); 10.1 (1H, br s).
6		1		519	¹ H NMR d (d6-DMSO): 5.2 (4H, s); 6.95 (1H, m); 7.25 (2H, m); 7.4 (5H, m); 7.5 (2H, m); 7.55 - 7.65 (4H, m); 7.9 (2H, m); 8.2 (1H, s); 10.3 (1H, br s).
7		1		577	V. espectro deficiente

* Para Ejemplos KK₁ y KK₃, los intermedios de éster se prepararon por ruta 1:



¹H NMR δ (d₆-DMSO): 3.8 (3H, s); 5.25 (4H, s); 6.95 (1H, t); 7.25 (2H, d); 7.4 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 8.0 (4H, q); 10.6 (1H, br s).

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^1H NMR δ (d_6 -DMSO): 1.2 (3H, t); 3.6 (2H, s); 4.1 (2H, q); 5.25 (4H, s); 6.95 (1H, t); 7.2 (4H, m); 7.4 (4H, m); 7.5 (2H, m); 7.6 (2H, m); 7.7 (2H, m); 10.15 (1H, br s).

EJEMPLO LL:

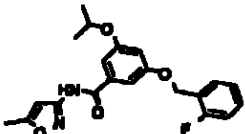
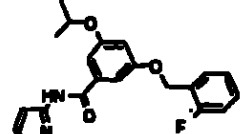
Por métodos análogos a los descritos más arriba se elaboraron también los siguientes compuestos, Ejemplos número LL₁ a LL₃.

Ejemplo	Estructura	Ruta	ME-HL	ME-HL	NMR
1		1a	360		
2		1a	382		
3		1a	412		

EJEMPLO MM:

Por métodos análogos a los descritos más arriba se elaboraron también los siguientes compuestos, Ejemplos números MM₁ a MM₂.

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Ejemplo	Estructura	Ruta	ME (g)	ME (g)	NMR
1		1a	385		
2		1a	371		

BIOLÓGICOS

Análisis:

Los efectos biológicos de los compuestos de Fórmula (I) o (IA) o (IB) pueden analizarse en la siguiente forma:

(1) La actividad enzimática de la GLK puede medirse incubando GLK, ATP y glucosa. La velocidad de formación de producto puede determinarse acoplando el ensayo a G-6-P dehidrogenasa, sistema NADP/NADPH y midiendo el aumento en la densidad óptica a 340nm (Matschinsky y *colegas* 1993).

(2) Un estudio de fijación a receptores GLK/GLKRP para medir las interacciones de unión entre GLK y GLKRP. El método puede utilizarse para identificar compuestos que modulan GLK modulando la interacción entre GLK y GLKRP. GLKRP y GLK se incuban con una concentración inhibidora de F-6-P, opcionalmente en la presencia del compuesto de prueba, y se mide la magnitud de interacción entre GLK y GLKRP. Compuestos que desplazan F-6-P o en cualquier otra forma reducen la interacción GLK/GLKRP se detectarán por una disminución en la cantidad de complejo GLK/GLKRP formado. Compuestos que promueven el la unión F-6-P o en cualquier otra forma mejoran la interacción GLK/GLKRP se detectarán por un aumento en la cantidad del complejo GLK/GLKRP

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D

formado. Un ejemplo específico de tal estudio de fijación de receptores se describe más adelante.

Análisis de proximidad de centelleo GLK/GLKRP

Se encontró que los compuestos A a S (descritos en Ejemplos A a S) y 1 a 118 (descritos en Ejemplos T a Y) tienen una actividad de por lo menos 40% de actividad a 10 μ m cuando se estudian en el análisis de proximidad de centelleo GLK/GLKRP descrito más adelante.

GLK humana recombinante GLK y GLKRP se usaron para desarrollar un SPA (análisis de proximidad de centelleo) de 96 pozos "mix and measure" ("mezclar y medir") como se describe en WO01/20327 (cuyo contenido se incorpora aquí por referencia). GLK (biotinilada) y GLKRP se incuban con perlas SPA enlazadas a estreptavidina (Amersham) en la presencia de una concentración inhibidora de [3H]F-6-P radiomarcada (Amersham Custom Synthesis TRQ8689), que emite una señal. Compuestos que desplazan la F-6-P o en cualquier otra forma trastornan la interacción de unión GLK / GLKRP harán que se pierda esta señal.

Se realizaron estudios de fijación a receptores a temperatura ambiente durante 2 horas. Las mezclas de reacción contenían 50mM Tris-HCl (pH 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, GLK biotinilada recombinante (0.1 mg), GLKRP recombinante (0.1 mg), 0.05mCi [3H] F-6-P (Amersham) para producir un volumen final de 100ml. Luego de la incubación, se determinó la magnitud de la formación del complejo GLK/GLKRP por la adición de 0.1mg/pozo de perlas SPA enlazadas a avidina (Amersham) y conteo de centelleo en un TopCount NXT Packard.

(3) Un estudio de fijación de receptores F-6-P / GLKRP para medir la interacción de unión entre GLKRP y F-6-P. Este método puede usarse para proporcionar información adicional sobre el mecanismo de acción de los compuestos. Los compuestos identificados en el estudio de fijación de receptores GLK/GLKRP pueden modular la interacción de GLK y GLKRP

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desplazando F-6-P o modificando la interacción GLK/GLKRP en alguna otra forma. Por ejemplo, generalmente se sabe que las interacciones proteína-proteína ocurren por interacciones a través de múltiples sitios de unión. En consecuencia es posible que un compuesto que modifica la interacción entre GLK y GLKRP pudiera actuar fijándose a uno o más de varios sitios de unión diferentes.

El estudio de fijación a receptores F-6-P / GLKRP identifica únicamente aquellos compuestos que modulan la interacción de GLK y GLKRP desplazando F-6-P de su sitio de unión en GLKRP.

GLKRP se incubaba con el compuesto de prueba y una concentración inhibidora de F-6-P, en la ausencia de GLK, y se mide la magnitud de la interacción entre F-6-P y GLKRP. Los compuestos que desplazan la fijación de F-6-P a GLKRP pueden detectarse por un cambio en la cantidad de complejo GLKRP/F-6-P formado. Un ejemplo específico de tal estudio de fijación a receptores se describe más adelante.

Análisis de proximidad de centelleo F-6-P / GLKRP

Se usó GLKRP humana recombinante para desarrollar un análisis de proximidad de centelleo de 96 pozos *"mix and measure"* ("mezclar y medir") como se describe en WO01/20327 (cuyo contenido se incorpora aquí por referencia). GLKRP marcada FLAG *"FLAG-tagged"* se incubó con perlas SPA recubiertas de proteína A (Amersham) y un anticuerpo anti-FLAG en la presencia de una concentración inhibidora de [3H]F-6-P radiomarcada. Se genera una señal. Los compuestos que desplazan la F-6-P harán que esta señal se pierda. Una combinación de este análisis y el estudio de fijación a receptores GLK/GLKRP permitirá al observador identificar compuestos que alteran la interacción de unión GLK/GLKRP desplazando F-6-P.

Se realizaron estudios de fijación de receptores a temperatura ambiente durante 2 horas. Las mezclas de reacción contenían 50mM Tris-HCl (pH 7.5), 2mM ATP, 5mM MgCl₂, 0.5mM DTT, GLKRP FLAG

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tagged recombinante (0.1 mg), anticuerpo Anti-Flag M2 (0.2mg) (IBI Kodak), 0.05mCi [3H] F-6-P (Amersham) para producir un volumen final de 100ml. Luego de la incubación, se determinó la magnitud de formación del complejo F-6-P/GLKRP por adición 0.1mg/pozo de perlas SPA enlazadas proteína A (Amersham) y conteo de centelleo en un TopCount NXT Packard.

Producción de GLK recombinante y GLKRP:

Preparación de mARN

Se preparó mARN total de hígado humano por homogeneización Polytron en 4M guanidina isotiocianato, 2.5mM citrato, 0.5% Sarkosyl, 100mM b-mercaptoetanol, seguido por centrifugación a través de 5.7M CsCl, 25mM acetato de sodio a 135,000g (máx.) como se describe en Sambrook J, Fritsch EF & Maniatis T, 1989.

Poly A⁺ mARN se preparó directamente usando un kit de aislamiento mARN FastTrack™ (Invitrogen).

Amplificación PCR de GLK y secuencias cADN GLKRP

Se obtuvo GLK humana y cADN GLKRP por PCR de mARN hepático humano usando técnicas establecidas descritas en Sambrook, Fritsch & Maniatis, 1989. Se diseñaron cebadores PCR de acuerdo con GLK y secuencias cADN GLKRP mostradas en Tanizawa y *colegas* 1991 y Bonthron, D.T. y *colegas* 1994 (corregido posteriormente en Warner, J.P. 1995).

Clonado en vectores Bluescript II

GLK y cADN GLKRP se clonaron en E. coli usando pBluescript II, (Short y *colegas* 1998) un sistema vector de clonado recombinante similar al empleado por Yanisch-Perron C y *colegas* (1985), que comprendía un colEI-based replicon con un fragmento ADN polienlazante que contenía múltiples sitios de restricción única, flanqueados por secuencias de

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promotor bacteriófago T3 y T7; un origen de fago filamentoso de replicación y un gen marcador de resistencia al fármaco ampicilina.

Transformaciones

Transformaciones de E. Coli se llevaron generalmente a cabo por electroporación. Cultivos de 400 ml de cepas DH5a o BL21 (DE3) se reprodujeron 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 deionizada helada, se resuspendieron en 1ml 10% glicerol y se almacenaron en alícuotas a -70°C. Se desalinizaron las mezclas de ligación usando membranas Millipore V series™ tamaño de poro (0.0025mm)). Se incubaron 40ml de células con 1ml de mezcla de ligación de ADN plásmido en hielo durante 10 minutos en cubetas de electroporación 0.2cm, y luego se pulsaron utilizando un aparato Gene Pulser™ (BioRad) a 0.5kVcm⁻¹, 250mF, 250?. Los transformantes se seleccionaron en L-agar suplementado con tetracilina a 10mg/ml o ampicilina a 100mg/ml.

Expresión

Se expresó GLK del vector pTB375NBSE en células de E.coli BL21, produciendo una proteína recombinante que contenía una etiqueta 6-His inmediatamente adyacente a la metiotina N-terminal. Alternativamente, otro vector apropiado es pET21(+)-DNA, Novagen, No. Cat 697703. Se utilizó la etiqueta 6-His para permitir la purificación de la proteína recombinante en una columna empacada níquel-ácido nitrilotriacético azarosa adquirida de Qiagen (No. Cat 30250).

Se expresó GLKRP del vector pFLAG CTC (IBI Kodak) en células de E.coli BL21, produciendo una proteína recombinante que contenía una etiqueta FLAG C-terminal. La proteína se purificó inicialmente por intercambio de iones de sefarosa DEAE seguida por la utilización de la etiqueta FLAG para purificación final en una columna de inmunoafinidad anti-FLAG M2 adquirida de Sigma-Aldrich (No. Cat A1205).

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Biotinilación de GLK:

Se biotiniló GLK por reacción con biotinamidocaproato N-hidroxisuccinimida éster (biotina-NHS) adquirida de Sigma-Aldrich (No. Cat B2643). Brevemente, grupos amino libres de la proteína diana (GLK) se hacen reaccionar con biotina-NHS con una relación molar definida que forma enlaces amida estables que resultan en un producto que contiene biotina covalentemente ligada. El exceso, biotina-NHS no-conjugada, se retira del producto por diálisis. Específicamente, se agergaron 7.5mg de GLK a 0.31 mg de biotina-NHS en 4mL de 25mM HEPES pH7.3, 0.15M KCl, 1mM ditiotreitól, 1mM EDTA, 1mM MgCl₂ (tampón A). Esta mezcla de reacción se dializó contra 100mL de tampón A que contenía 22mg adicionales de biotina-NHS. Después de 4 horas se retiró el exceso de biotina-NHS por una diálisis extensiva contra el tampón A.

COMPOSICIONES FARMACÉUTICAS

Las siguientes ilustran formas farmacéuticas representativas de la invención como se definen aquí (designándose el ingrediente activo "Compuesto X"), para uso terapéutico o profiláctico en humanos:

(a)	<u>Tableta I</u>	<u>Mg/tableta</u>
	Compuesto X	100
	Lactosa Ph.Eur	182.75
	Croscarmelosa sódica.....	12.0
	Pasta de almidón de maíz (5% p/v pasta).....	2.25
	Estearato de magnesio.....	3.0

(b)	<u>Tableta II</u>	<u>Mg/tableta</u>
	Compuesto	X 50
		

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Lactosa Ph.Eur	223.75
Croscarmelosa sódica.....	6.0
Almidón de maíz	15.0
Polivinilpirrolidona (5% p/v pasta).....	2.25
Estearato de magnesio.....	3.0

(c) Tableta III Mg/tableta

Compuesto X 1.0

.....

Lactosa Ph.Eur	93.25
Croscarmelosa sódica.....	4.0
Pasta de almidón de maíz (5% p/v pasta).....	0.75
Estearato de magnesio.....	1.0

(d) Capsula Mg/capsula

Compuesto X 10

Lactosa Ph.Eur 488.5

Magnesio 1.5

(e) Inyección I (50 mg/ml)

Compuesto X 5.0% p/v

1M Solución de hidróxido de sodio..... 15.0% v/v

0.1M ácido clorhídrico (para ajustar pH a 7.6)

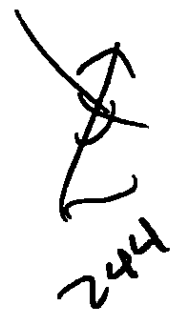
Polietilen glicol 400..... 4.5% p/v

Agua para inyección a 100%

(f) Inyección II (10 mg/ml)

Compuesto X 1.0% p/v

Fosfato de sodio BP 3.6% p/v



0.1M Solución de hidróxido de sodio..... 15.0% v/v
Agua para inyección a 100%

(g) Inyección III (1 mg/ml, tamponada a pH6)

Compuesto X 0.1% p/v
Fosfato de sodio BP 2.26% p/v
Ácido cítrico..... 0.38% p/v
Polietilen glicol 400..... 3.5% p/v
Agua para inyección a 100%

(h) Aerosol I mg/ml

Compuesto X 10.0
Trioleato de sorbitán..... 13.5
Triclorofluorometano 910.0
Diclorodifluorometano 490.0

(i) Aerosol II mg/ml

Compuesto X 0.2
Trioleato de sorbitán..... 0.27
Triclorofluorometano 70.0
Diclorodifluorometano 280.0
Diclorotetrafluoroetano 1094.0

(j) Aerosol III mg/ml

Compuesto X 205
Trioleato de sorbitán..... 3.38
Triclorofluorometano 67.5
Diclorodifluorometano 1086.0
Diclorotetrafluoroetano 191.6

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(k) <u>Aerosol IV</u>		<u>mg/ml</u>
Compuesto	X	2.5
.....		
Lecitina de soya.....		2.7
Triclorofluorometano		67.5
Diclorodifluorometano		1086.0
Diclorotetrafluoroetano		191.6
(l) <u>Ungüento</u>		<u>ml</u>
Compuesto X		40 mg
Etanol		300 µl
Agua		300 µl
1-Dodecilazacicloheptan-2-ona.....		50 µl
Propilen glicol.....		a 1 ml

Nota

Las formulaciones anteriores pueden obtenerse por procedimientos convencionales bien conocidos en el arte farmacéutico. Las tabletas (a)- (c) pueden proveerse de una cubierta gastrorresistente por medios convencionales, por ejemplo proveerse una cubierta de ftalato de acetato de celulosa. Las formulaciones de aerosol (h)- (k) pueden usarse en conjunción con dispensadores estándar de aerosol con dosis medidas, y los agentes de suspensión trioleato de sorbitán y lecitina de soya pueden sustituirse por un agente de suspensión alternativo tales como monooleato de sorbitán, sesquioleato de sorbitán, polisorbato 80, poliglicerol oleato o ácido oleico.

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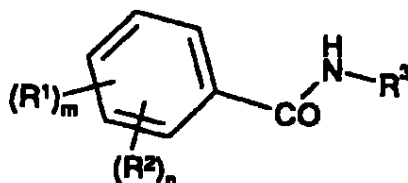
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6/1/2**REIVINDICACIONES:**

1. El uso de un compuesto de Fórmula (I) o una sal, solvato o profármaco del mismo, en la preparación de un medicamento para uso en el tratamiento o prevención de una enfermedad o condición médica mediada por GLK:



Fórmula (I)

en donde

m es 0, 1 ó 2;

n es 0, 1, 2, 3 ó 4;

cada R^1 se selecciona independientemente de OH, $-(CH_2)_{1-4}OH$, $-CH_2-F$, $-(CH_2)_{1-4}CH_2-F$, $-OCH_2-F$, halo, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, NH_2 , $-NH-C_{1-4}$ alquilo, $-N-di-(C_{1-4}$ alquil), CN, formilo, fenilo o heterociclilo sustituido opcionalmente por C_{1-6} alquilo;

cada R^2 es el grupo Y-X-

en donde cada X es un enlazante seleccionado independientemente de:

$-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-(CH_2)_{1-4}-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$, $-Z-$, $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z-$, $-O-Z-N(R^6)-Z-$, $-O-C(O)-Z-O-Z-$ o un enlace directo;

cada Z es independientemente un enlace directo, C_{2-6} alquenileno o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$;

cada Y se selecciona independientemente de aril- Z^1- , heterociclil- Z^1- ,

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C_{3-7} cicloalquil- Z^1 -, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, - $(CH_2)_{1-4}$ CH_3 - F_n o - $CH(OH)CH_3$ - F_n ; en donde cada Y se sustituye independientemente en forma opcional por hasta 3 grupos R^4 ;

cada R^4 se selecciona independientemente de halo, - CH_3 - F_n , CN, NH_2 , C_{1-6} alquilo, - OC_{1-6} alquilo, -COOH, - $C(O)OC_{1-6}$ alquilo, OH o fenil sustituido opcionalmente por C_{1-6} alquilo o - $C(O)OC_{1-6}$ alquilo,

o R^5 - X^1 -, donde X^1 es independientemente como se define en X más arriba y R^5 se selecciona de hidrógeno.

C_{1-6} alquilo, - CH_3 - F_n , fenilo, naftilo, heterociclilo o C_{3-7} cicloalquilo; y R^5 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: halo, C_{1-6} alquilo, OC_{1-6} alquilo, - CH_3 - F_n , CN, OH, NH_2 , COOH, o - $C(O)OC_{1-6}$ alquilo,

cada Z^1 es independientemente un enlace directo, C_{2-6} alquenileno o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q$;

R^3 se selecciona de fenilo o un heterociclilo, y R^3 se sustituye opcionalmente por uno o más R^7 groups.

R^6 se selecciona independientemente de hidrógeno, C_{1-6} alquilo o - C_{2-4} alquil-O- C_{1-4} alquilo;

R^{6a} se selecciona independientemente de hidrógeno, halo, C_{1-6} alquilo o - C_{2-4} alquil-O- C_{1-4} alquilo;

cada R^7 se selecciona independientemente de:

C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, $(CH_2)_{0-3}$ arilo, $(CH_2)_{0-3}$ heterociclilo, $(CH_2)_{0-3}$ C_{3-7} cicloalquilo, OH, C_{1-6} alquilo, OH, halo, C_{1-6} alquil-halo, OC_{1-6} alquilo, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3 , tioxo, NH_2 , CN, $(CH_2)_{0-3}NHSO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}-O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$; $(CH_2)_{0-3}C(O)NHSO_2-R^8$ y $(CH_2)_{0-3}$

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$_3\text{SO}_2\text{NHC(O)-R}^8$ en donde una cadena alquilo, anillo cicloalquilo o anillo heterociclilo dentro de R^7 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, $-\text{OH}$, halo, CN , NH_2 , N-C_{1-4} alquilamino, N,N-di-C_{1-4} alquilamino y OC_{1-4} alquilo;

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, arilo, heterociclilo, C_{3-7} cicloalquilo, OH , C_{1-6} alquil- OH , COOH , C(O)OC_{1-6} alquilo, $\text{N(R}^6\text{)C}_{1-6}$ alquilo, OC_{1-6} alquilo, C_{0-6} alquil OC(O)C_{1-6} alquilo, $\text{C(OH)(C}_{1-6}\text{alquil)C}_{1-6}$ alquilo; en donde una cadena alquilo o arilo, heterociclilo o anillo cicloalquilo dentro de R^8 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, OH , halo, CN , NH_2 , $-\text{NH-C}_{1-4}$ alquilo, $-\text{N-di-(C}_{1-4}\text{alquil)}$ y OC_{1-4} alquilo,

cada a es independientemente 1, 2 ó 3;

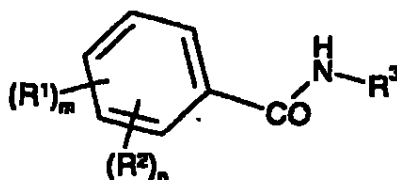
p es un entero entre 0 y 3;

q es un entero entre 0 y 3;

y $p + q < 4$.

con la condición que cuando R^3 es 2-piridilo y X es distinto a $-\text{Z}-$, $-\text{C(O)-Z-O-Z-}$, $-\text{N(R}^6\text{)-C(O)-Z-O-Z-}$ ó $-\text{O-Z-N(R}^6\text{)-Z-}$, entonces R^3 no puede ser mono-sustituido en la posición 5- con un grupo R^7 seleccionado de COOH ó C(O)OC_{1-6} alquilo.

2. Una composición farmacéutica que comprende un compuesto de Fórmula (I) como se reivindica en la Reivindicación 1, o una sal, solvato o profármaco del mismo, junto con un diluyente o transportador farmacéuticamente aceptable para uso en la preparación de un medicamento para uso en el tratamiento o prevención de una enfermedad o condición médica mediada por GLK.
3. Un compuesto de Fórmula (Ib) o una sal, solvato o profármaco del mismo



Formula (Ib)

en donde

m es 0, 1 ó 2;

n es 1, 2, ó 3;

y $n + m$ es 2 ó 3;

cada R^1 se selecciona independientemente de OH, $-(CH_2)_{1-4}OH$, CH_3F_n , $(CH_2)_{1-4}CH_3F_n$, OCH_3F_n , halo, OCH_3 , C_2H_5O , $CH_3C(O)O-$, C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, NH, C_{1-4} alquilo, -N-di- $(C_{1-4}$ alquil), CN, formilo, fenilo o heterociclilo sustituido opcionalmente por C_{1-6} alquilo;

cada R^2 es el grupo $Y-X-$

con la condición que Y-X no puede ser CH_3O , C_2H_5O ó $CH_3C(O)O-$

en donde cada X es un enlazante seleccionado independientemente de

$-O-Z-$, $-O-Z-O-Z-$, $-C(O)O-Z-$, $-OC(O)-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)SO_2-Z-$, $-SO_2N(R^6)-Z-$, $-CH=CH-Z-$, $-C\equiv C-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-C(O)N(R^6)S(O)_2-Z-$, $-S(O)_2N(R^6)C(O)-Z-$, $-C(O)-Z-$, $-Z-$, $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z-$, $-O-Z-N(R^6)-Z-$, $-O-C(O)-Z-O-Z-$ o un enlace directo excepto donde Z es C_{1-6} alquilo;

cada Z es independientemente un enlace directo, C_{2-6} alquenileno o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$;

cada Y se selecciona independientemente de aril- Z^1- , heterociclil- Z^1- , C_{3-7} cicloalquil- Z^1- , C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, $-(CH_2)_{1-4}CH_3F_n$ o $-CH(OH)CH_3F_n$; en donde cada Y se sustituye independientemente en forma opcional por hasta 3 grupos R^4 ;

cada R^4 se selecciona independientemente de halo, $-CH_3F_n$, CN, NH_2 , C_{1-4} alquilo, $-OC_{1-6}$ alquilo, $-COOH$, -

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$C(O)OC_{1-6}$ alquilo, OH o fenilo sustituido opcionalmente por C_{1-6} alquilo o $-C(O)OC_{1-6}$ alquilo,

o R^5-X^1 -, donde X^1 es independientemente como se define en X más arriba y R^5 se selecciona de hidrógeno, C_{1-6} alquilo, $-CH_2F$, fenilo, naftilo, heterociclilo o C_{3-7} cicloalquilo; y R^5 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: halo, C_{1-6} alquilo, OC_{1-6} alquilo, $-CH_2F$, CN, OH, NH_2 , COOH, o $-C(O)OC_{1-6}$ alquilo,

cada Z^1 es independientemente un enlace directo, C_2 alquenileno o un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q$;

R^3 es heterociclilo, en donde el átomo en la posición 2 del anillo heterociclilo relative al grupo amida, al cual se une R^3 , es un heteroátomo y cuando el átomo en la posición 2 del anillo heterociclilo relative al grupo amida es nitrógeno, éste es un nitrógeno hibridado sp^2 , y R^3 se sustituye opcionalmente por hasta 2 grupos R^7 ;

R^6 se selecciona independientemente de hidrógeno, C_{1-6} alquilo o $-C_2$ alquil-O- C_{1-4} alquilo;

R^{6a} se selecciona independientemente de hidrógeno, halo, C_{1-6} alquilo o $-C_2$ alquil-O- C_{1-4} alquilo;

cada R^7 se selecciona independientemente de:

C_{1-6} alquilo, C_2 alquenilo, C_2 alquinilo, $(CH_2)_{0-3}$ arilo, $(CH_2)_{0-3}$ heterociclilo, $(CH_2)_{0-3}C_{3-7}$ cicloalquilo, OH, C_{1-6} alquilo, OH, halo, C_{1-6} alquil-halo, OC_{1-6} alquilo, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3 , tioxo, NH_2 , CN, $(CH_2)_{0-3}NHSO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}-O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$; $(CH_2)_{0-3}C(O)NHSO_2-R^8$ y $(CH_2)_{0-3}SO_2NHC(O)-R^8$ en donde una cadena alquilo, anillo cicloalquilo o anillo heterociclilo dentro de R^7 se sustituye opcionalmente por uno

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X
Y
Z

o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, -OH, halo, CN, NH_2 , $N-C_{1-4}$ alquilamino, N,N -di- C_{1-4} alquilamino y OC_{1-4} alquilo;

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, arilo, heterociclilo, C_{3-7} cicloalquilo, OH, C_{1-6} alquil-OH, COOH, $C(O)OC_{1-6}$ alquilo, $N(R^6)C_{1-6}$ alquilo, OC_{1-6} alquilo, C_{0-6} alquilOC(O) C_{1-6} alquilo, $C(OH)(C_{1-6}alquil)C_{1-6}alquilo$; en donde una cadena alquilo o arilo, heterociclilo o anillo cicloalquilo dentro de R^8 se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, OH, halo, CN, NH_2 , -NH- C_{1-4} alquilo, -N-di-(C_{1-4} alquil) y OC_{1-4} alquilo,

cada a es independientemente 1, 2 ó 3;

p es un entero entre 0 y 3;

q es un entero entre 0 y 3;

y $p + q < 4$;

con la condición que

- (i) cuando R^3 es 2-piridilo y X es distinto a -Z-, $-C(O)-Z-O-Z-$, $-N(R^6)-C(O)-Z-O-Z$ o $O-Z-N(R^6)-Z$, entonces R^3 no puede ser mono-sustituido en la posición 5 con un grupo R^7 seleccionado de COOH o $C(O)OC_{1-6}$ alquilo;
- (ii) las posiciones 3,5 en el anillo fenilo (al cual se unen R^1 y R^2) relativo al enlace amida son sustituidas y por lo menos uno de los grupos en la posición 3 y 5 es un grupo R^2 ;
- (iii) una cadena C_{1-6} alquilo no sustituido, no ramificada no puede exceder en longitud a un C_6 alquilo;
- (iv) cuando n es 2 ó 3, entonces únicamente un grupo X puede ser -NHC(O)-;
- (v) cuando R^3 es piridilo y R^7 es halo o metilo, entonces el anillo fenilo al cual se une R^2 no puede ser sustituido por un grupo R^2 en la posición 2- relativa al enlace amida en donde X es $-C(O)NH-$ y Y es fenilo opcionalmente sustituido, tienilo opcionalmente sustituido o piridilo opcionalmente sustituido;

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- (vi) cuando $n+m$ es 2, m es 0 ó m es 1 y R^1 es OH, n es 1 y X es -NHC(O)- ó n es 2 y X se selecciona independientemente de -C(O)NH-, -NHC(O)-, -O-, -S(O₂)NH- o un enlace directo en donde un grupo X es -NHC(O), Y se selecciona de fenilo, ciclohexilo, 4,5-dihidro-5-oxo-pirazolilo, tienilo, 1,3-dihidro-1,3-dioxo-isoindolinilo, 2-oxo 1-benzopirano o piridilo y Y se sustituye opcionalmente por R^4 , entonces R^3 no puede ser tiazol no sustituido, 4,5-dihidro-5-oxo-pirazolilo sustituido por triclorofenilo, 4,5,6,7-tetrahidro-benzo[b]tiofeno sustituido por etoxicarbonilo o piridilo opcionalmente de manera independiente mono o di-sustituido por metilo, etoxi o propilcarbonilamino; y
- (vii) cuando $n+m$ es 3, m es 0 o 2, R^1 se selecciona independientemente de metilo, metoxi o hidroxilo, n es 1, 2 ó 3, X se selecciona independientemente de -O-, -S(O₂)NH-, -C(O)-, -S(O₂)-, -CH₂- o un enlace directo, Y se selecciona de pirrolidinilo, morfolino, fenilo, tetrazolilo o propilo en donde Y se sustituye opcionalmente por R^4 y R^4 se selecciona de di-hidroxilo, metoxi, C₁₋₄alquilo entonces R^3 no puede ser tetrazolilo, tiazolilo no sustituido o tiazolilo sustituido por etoxicarbonilmetilo.
4. Un compuesto de acuerdo con la Reivindicación 3, o una sal, solvato o profármaco del mismo, en donde cada R^1 se selecciona independientemente de OH, formilo, CH₃₋₄F₂, OCH₃₋₄F₂, halo, C₁₋₆alquilo, NH₂, CN, (OH₂)₁₋₄OH o un heterociclilo opcionalmente sustituido por C₁₋₆alquilo;
5. A compuesto de acuerdo con la Reivindicación 3 o Reivindicación 4, o una sal, solvato o profármaco del mismo, en donde cada R^2 es el grupo Y-X-, cada X se selecciona independientemente de -Z-, -CH=CH-Z-, -O-Z-, -C(O)-Z-, -C(O)O-Z-, -OC(O)-Z-, -C(O)-Z-O-Z-, -O-C(O)-Z-O-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R⁶)-Z-, -N(R⁶)CO-Z-, -CON(R⁶)-Z-, -N(R⁶)-C(O)-Z-O-Z-, -SO₂N(R⁶)-Z-, -N(R⁶)SO₂-Z- ó -

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O-Z-N(R⁶)-Z-; cada Y se selecciona independientemente de C₁₋₆alquilo, C₂₋₆alquenilo, aril-Z¹-, heterociclil-Z¹-C₃₋₇cicloalquil(CH₂)₀₋₂-, -(CH₂)₁₋₄CH₃₋₄F₁₋₄ y cada Y se sustituye independientemente en forma opcional por R⁴.

6. Un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 5, o una sal, solvato o profármaco del mismo, en donde cada R⁴ se selecciona independientemente de halo, CH₃₋₄F₁₋₄, OCH₃₋₄F₁₋₄, CN, C₁₋₆alquilo, OC₁₋₆alquilo, COOH, C(O)OC₁₋₆alquilo, (CH₂)₀₋₃COOH, O(CH₂)₀₋₃COOH, CO-fenilo, CONH₂, CONH-fenilo, SO₂NH₂, SO₂C₁₋₆alquilo, OH, o fenilo opcionalmente sustituido por uno o más grupos R⁵ donde R⁵ se selecciona de hidrógeno, C₁₋₆alquilo o C(O)OC₁₋₆alquilo;
7. Un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 6, o una sal, solvato o profármaco del mismo, en donde R³ es un heterociclilo con contenido de nitrógeno, sustituido opcionalmente por uno o más grupos R⁷.
8. Un compuesto de acuerdo con la Reivindicación 7, o una sal, solvato o profármaco del mismo, en donde R³ se selecciona de tiazol, benzotiazol, tiadiazol, piridina, pirazina, piridazina, pirazol, imidazol, pirimidina oxazol e indol.
9. Un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 8, o una sal, solvato o profármaco del mismo, en donde R³ se sustituye o no se sustituye por un grupo R⁷.
10. Un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 9, o una sal, solvato o profármaco del mismo, en donde cada R⁷ se selecciona independientemente de OH, CN, NH₂, SO₃, tioxo, halo,

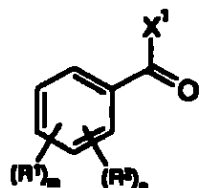
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C_{1-4} alquilo, C_{1-4} alquil-OH, O- C_{1-4} alquilo, C_{1-4} alquil-halo, $(CH_2)_{0-1}COOH$, $(CH_2)_{0-1}C(O)OR^8$, $(CH_2)_{0-1}NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}NHC(O)(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$, $-(CH_2)_{0-2}S(O)_{0-2}R^8$, $-(CH_2)_{0-1}N(R^6)SO_2R^8$, $(CH_2)_{0-1}C(O)N(R^6)S(O)_2R^8$ ó $(CH_2)_{0-1}$ heterociclilo.

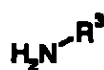
11. Un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 10, o una sal, solvato o profármaco del mismo, en donde Y es fenil- Z^1 - sustituido opcionalmente por halo o C_{1-6} alquilo.
12. Un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 11, o una sal, solvato o profármaco del mismo, en donde cada R^2 es el grupo Y-X-, Z en la definición de X es un enlace directo y Z^1 en la definición de Y es un grupo de la fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$.
13. Una composición farmacéutica que comprende un compuesto de acuerdo con una cualquiera de las Reivindicaciones 3 a 12 o una sal, solvato o profármaco del mismo, junto con un diluyente o transportador farmacéuticamente aceptable.
14. El uso de un compuesto de Fórmula (I), como se define en la Reivindicación 1, o una sal, solvato o profármaco del mismo, en la preparación de un medicamento para uso en el tratamiento combinado o prevención de diabetes y obesidad.
15. El uso de un compuesto de Fórmula (Ib) o una sal, solvato o profármaco del mismo, como se define en la Reivindicación 3, como un medicamento.
16. Un proceso para la preparación de un compuesto de Fórmula (I), o una sal, solvato o profármaco del mismo, como se define en la Reivindicación 1, que comprende:

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- (a) reacción de un compuesto de Fórmula (IIIa) con un compuesto de Fórmula (IIIb),



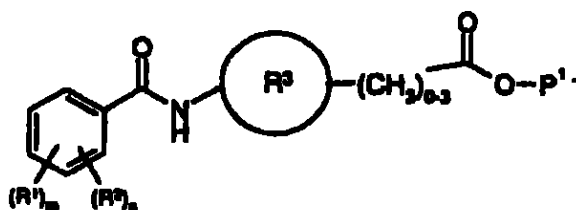
Fórmula (IIIa)



Fórmula (IIIb); o

en donde X¹ es un grupo saliente

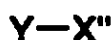
- (b) para compuestos de Fórmula (I) en donde R³ es hidrógeno, desprotección de un compuesto de Fórmula (IIIc),



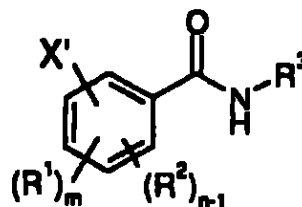
Fórmula (IIIc)

en donde P¹ es un grupo protector;

- (c) para compuestos de Fórmula (I) en donde n es 1, 2, 3 ó 4, reacción de un compuesto de Fórmula (IIId) con un compuesto de Fórmula (IIIe),



Fórmula (IIId)



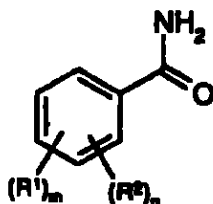
Fórmula (IIIe)

en donde X' y X'' comprenden grupos que cuando se hacen reaccionar juntos forman el grupo X;

- (d) para un compuesto de Fórmula (I) en donde n es 1, 2, 3 ó 4 y X o X¹ es -SO-Z- o -SO₂-Z-, oxidación del correspondiente compuesto de Fórmula (I) en donde X o X¹ respectivamente es -S-Z-;
- (e) reacción de un compuesto de Fórmula (IIIf) con un

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compuesto de Fórmula (IIIg),



Fórmula (III f)



Fórmula (III g); o

en donde X^2 es un grupo saliente

y, a partir de entonces, si es necesario:

- i) convertir un compuesto de Fórmula (I) en otro compuesto de Fórmula (I);
- ii) retirar los grupos protectores;
- iii) formar una sal, pro-fármaco o solvato del mismo.

TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES

Remitente:

OFICINA ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

A:

BRYANT, Tracey
ASTRAZENECA
Global Intellectual Property
Meraside, Alderley Park
Macclesfield
Cheshire SK10 4TG
GRAN BRETAÑA

PCT

COMUNICACIÓN SOBRE EL ENVÍO DEL
INFORME DE EXAMEN PRELIMINAR
INTERNACIONAL

(Regla 71.1 PCT)

Fecha de envío
(Día/Mes/Año)

03/08/2003

No. de Expediente del Solicitante o Apoderado

100379/WO

COMUNICACIÓN IMPORTANTE

No. de Solicitud Internacional

PCT / GB 02/ 03745

Fecha Internacional de Presentación
(día/mes/año)

15/08/2002

Fecha de Prioridad
(día/mes/año)

17/08/2001

Solicitante

ASTRAZENECA AB et al.

1. Se comunica al solicitante que la oficina encargada del examen preliminar internacional le envía con el presente el Informe de examen preliminar internacional, elaborado para la solicitud internacional, en caso dado con los anexos correspondientes.
2. Una copia del Informe, en caso dado con los anexos correspondientes se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas seleccionadas.
3. A solicitud de una oficina seleccionada, la Oficina Internacional preparará una traducción del informe (pero no de los anexos) al inglés y la remitirá a esta oficina.

4 RECORDATORIO

Para ingresar en la fase nacional el solicitante, dentro de los 30 meses a partir de la fecha de prioridad (o en algunas oficinas incluso después), tiene que realizar ante cada oficina seleccionada ciertos actos (entrega de traducciones y desembolso de honorarios nacionales) (Artículo 39 (1)) (véase también la información remitida por la Oficina Internacional en el Formulario PCT/IB/301).

Si se tiene que enviar a una oficina seleccionada una traducción de la solicitud internacional, entonces esta traducción tiene que incluir traducciones de todos los anexos al Informe de examen preliminar internacional. Es obligación del solicitante elaborar dichas traducciones y hacerlas llegar directamente a las oficinas seleccionadas respectivas.

Mayores detalles en cuanto a los plazos normativos y los requisitos de las oficinas seleccionadas se desprenden del Volumen II de la guía PCT para solicitantes.

Se llama la atención del solicitante al Artículo 33(5), que establece que los criterios de novedad, actividad inventiva y posibilidad de aplicación industrial descritos en Artículo 33(2) a (4) sirven meramente los propósitos del examen preliminar internacional y que Todo Estado Contratante puede aplicar criterios adicionales o diferentes para efectos de decidir si la invención reivindicada es patentable o no (véase también Artículo 27 (5)). Los criterios adicionales pueden incluir, por ejemplo, exención de patentabilidad y los requerimientos, si se permite la divulgación, y de claridad y sustento de las reivindicaciones.

Nombre y dirección postal de la Oficina Encargada del
Examen Preliminar Internacional IPEA

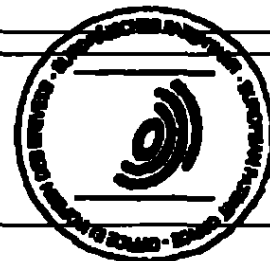


Oficina Europea de Patentes
D-80298 Munich
Tel.: (+ 49-89) 2369-0, Tx: 523856 epmu d
Fax: (+ 49-89) 2369-4465

Empleado Autorizado

LODOLO F

Tel.: (+ 49-89) 2369 2828



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**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES**

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 38 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado 100379/WO	PROCEDIMIENTO POSTERIOR véase comunicación sobre el envío del informe de examen preliminar internacional (Formulario PCT/IPEA/418)	
No. de Expediente Internacional PCT / GB 02/ 03745	Fecha Internacional de Presentación (día/mes/año) 15/08/2002	Fecha de Prioridad (día/mes/año) 17/08/2001
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC A61K31 / 425		
Solicitante ASTRAZENECA AB et al.		

1. Este informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 38.

2. Este INFORME comprende un total de 2 hojas, inclusive esta portada

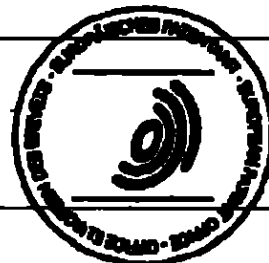
☐ Además se adjuntan ANEXOS al informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.18 y Sección 607 de las Instrucciones administrativas al PCT).

Estos anexos comprenden en total de _____ hojas.

3. Este informe contiene datos con respecto a los siguientes puntos:

- I ☒ Base del Informe
- II ☐ Prioridad
- III ☒ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial
- IV ☐ Uniformidad deficiente de la invención
- V ☒ Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración
- VI ☐ Ciertos documentos enumerados
- VII ☐ Ciertas deficiencias del registro internacional
- VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 18/02/2003	Fecha de la conclusión de este informe 28/05/2003
Nombre y dirección postal de la Oficina Encargada del Examen Preliminar Internacional IPEA  Oficina Europea de Patentes D-80298 Munich Tel.: (+ 49-89) 2399-0, Tx: 523856 epmu d Fax: (+ 49-89) 2399-4486	Empleado Autorizado TZSCHOPPE D A Tel.: (+ 49-89) 2399 2828



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I. Base del Informe

La base de este informe de examen preliminar la constituye la solicitud tal como se radicó originalmente.

III. Ausencia de formulación de opinión en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial

La cuestión de si la invención reivindicada parece ser novedosa, implicar una actividad inventiva o ser aplicable industrialmente no ha sido objeto del examen preliminar internacional con respecto a las reivindicaciones que no se han investigado (Artículo 17(2) (a) ó (3) y Regla 66.1 (e) PCT); véase también el informe de búsqueda internacional).

V. Declaración motivada bajo Regla 66.2(a)(II) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial

En la medida en que se ha llevado a cabo el examen preliminar internacional (véase ítem III más arriba en el texto), se señala lo siguiente:

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como se define en por lo menos algunas de las reivindicaciones, que han sido objeto de un informe de búsqueda internacional, no parece satisfacer los criterios mencionados en Artículo 33(1) PCT, es decir, no parece ser novedosa y/o implicar actividad inventiva (véase informe de búsqueda internacional, en particular los documentos citados X y/o Y y referencias a las reivindicaciones correspondientes).

262 3 92
The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EPO

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 100379/WO	
International application No. PCT/GB02/03745	International filing date (day/month/year) 15 August 2002 (15.08.02)	(Earliest) Priority date (day/month/year) 17 August 2001 (17.08.01)	
Title of invention COMPOUNDS EFFECTING GLUCOKINASE			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB S-151 85 Södertälje Sweden		Telephone No. +44 1625 230148	
		Facsimile No. +44 1625 510752	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: SE		State (that is, country) of residence: SE	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) ASTRAZENECA UK LIMITED 15 Stanhope Gate London, Greater London W1Y 6LN United Kingdom			
State (that is, country) of nationality: GB		State (that is, country) of residence: GB	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BOYD, Scott Alderley Park Macclesfield Cheshire, SK10 4TG United Kingdom			
State (that is, country) of nationality: GB		State (that is, country) of residence: GB	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

JOHNSTONE, Craig
Alderley Park
Macclesfield
Cheshire, SK10 4TG
United Kingdom

State (that is, country) of nationality:
GBState (that is, country) of residence:
GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

JONES, Clifford, David
Alderley Park
Macclesfield
Cheshire, SK10 4TG
United Kingdom

State (that is, country) of nationality:
GBState (that is, country) of residence:
GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MCKERRECHER, Darren
Alderley Park
Macclesfield
Cheshire, SK10 4TG
United Kingdom

State (that is, country) of nationality:
GBState (that is, country) of residence:
GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BLOCK, Michael, Howard
35 Gatehouse Drive
Waltham, MA 02451
Cheshire, SK10 4TG
United States of America

State (that is, country) of nationality:
GBState (that is, country) of residence:
US☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)BRYANT, Tracey, et al
ASTRAZENECA
Global Intellectual Property
Mersey, Alderley Park
Macclesfield,
Cheshire, SK10 4TG
United Kingdom

Telephone No.

+44 1625 513228

Facsimile No.

+44 1625 510752

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (<i>specify</i>) | : | sheets |

For International Preliminary Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (<i>specify</i>): |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

.....
BRYANT, Tracey, et al

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/GB02/03745 Applicant's or agent's file reference 100379/WO Applicant AstraZeneca AB et al CALCULATION OF PRESCRIBED FEES 1. Preliminary examination fee EURO 1530.00 P 2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>) EURO 159.00 H 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box EURO 1689.00 TOTAL	For International Preliminary Examining Authority use only Date stamp of the IPEA								
MODE OF PAYMENT <table style="width: 100%;"> <tr> <td>☒ authorization to charge deposit account with the IPEA (see below)</td> <td>☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>		☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash								
☐ cheque	☐ revenue stamps								
☐ postal money order	☐ coupons								
☐ bank draft	☐ other (specify):								
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (<i>This mode of payment may not be available at all IPEAs</i>) ☒ Authorization to charge the total fees indicated above. ☒ (<i>This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i>) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. IPEA/ <u>EPO</u> Deposit Account No.: <u>2810 0023</u> Date: <u>14th February 2003</u> Name: <u>Jennifer C Bennett</u> Signature: _____									

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 02/03745

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/425 C07D417/12 C07D233/48 C07D285/12 C07D213/75
C07D241/20 C07D231/40 C07D237/20 C07D239/42 C07D307/66
A61P03/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07D

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

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

CHEM ABS Data, PAJ, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevance to claim No.
X	FORD, ROGER E. ET AL: "Synthesis and quantitative structure-activity relationships of antiallergic 2-hydroxy-N-(1H-tetrazol-5-yl)benzamides and N-(2-hydroxyphenyl)-1H-tetrazole-5-carboxamides" J. MED. CHEM. (1986), 29(4), 538-49 , XP001026086 formula 2 table 1 — — / —	3

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

10 October 2002

Date of mailing of the international search report

23/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Palatinen 2
NL - 2200 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 851 epo nl
Fax (+31-70) 340-3016

Authorized officer

Seelmann, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 02/03745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	ZHANG, SAN-QI ET AL: "Synthesis based on affinity separation (SAS): separation of products having barbituric acid tag from untagged compounds by using hydrogen bond interaction" SYNLETT (2001), (5), 590-596 , XP001106577 page 591	3
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 06, 31 March 1999 (1999-03-31) -& JP 08 173525 A (LADD LELAND L), 9 July 1996 (1996-07-09) abstract	3
X	US 4 146 631 A (MARSHALL STUART M ET AL) 27 March 1979 (1979-03-27) column 2, line 17 -column 3, line 18; claim 1	3
X	WO 01 19788 A (COR THERAPEUTICS INC) 22 March 2001 (2001-03-22) claim 1; example 196	3
A	WO 01 44216 A (HOFFMANN LA ROCHE) 21 June 2001 (2001-06-21) cited in the application the whole document	1-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/03745

267 266

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 02 03745

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The present claims relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. For the present scope of claim 3 the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula (I) with R2 = O-CH2-Phenyl or O-CH2-CH2-Phenyl.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 02/03745

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 08173525	A	09-07-1996	US 5792109 A	11-08-1998
			EP 0699448 A1	06-03-1996
US 4146631	A	27-03-1979	GB 1561350 A	20-02-1980
			AU 514372 B2	05-02-1981
			AU 3031277 A	10-05-1979
			BE 860513 A1	05-05-1978
			CA 1094565 A1	27-01-1981
			DE 2749518 A1	18-05-1978
			DK 489777 A	06-05-1978
			FR 2370041 A1	02-06-1978
			HU 176842 B	28-05-1981
			IE 45723 B1	03-11-1982
			JP 1357474 C	13-01-1987
			JP 53059669 A	29-05-1978
			JP 61021233 B	26-05-1986
			LU 78459 A1	14-07-1978
			NL 7711901 A	09-05-1978
			ZA 7706555 A	30-08-1978
WO 0119788	A	22-03-2001	AU 7486600 A	17-04-2001
			AU 7486700 A	17-04-2001
			CZ 20020959 A3	17-07-2002
			EP 1216231 A2	26-06-2002
			EP 1216228 A2	26-06-2002
			NO 20021229 A	21-05-2002
			NO 20021230 A	21-05-2002
			WO 0119798 A2	22-03-2001
			WO 0119788 A2	22-03-2001
			US 2002091116 A1	11-07-2002
			AU 4535301 A	12-09-2001
			AU 5078301 A	12-09-2001
			NO 0164642 A2	07-09-2001
			NO 0164643 A2	07-09-2001
			US 2002002183 A1	03-01-2002
WO 0144216	A	21-06-2001	AU 2365201 A	25-06-2001
			WO 0144216 A1	21-06-2001
			EP 1242397 A1	25-09-2002
			NO 20022863 A	14-06-2002
			US 6353111 B1	05-03-2002

PCT REQUEST

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100379/WO

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-EASY Version 2.92 (updated 01.01.2003)
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	100379/WO
I	Title of invention	COMPOUNDS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	AP: (GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW); EA: (AM AZ BY KG KZ MD RU TJ TM); EP: (AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE 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 BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
II-4	Name	ASTRAZENECA AB
II-5	Address:	Sodertalje S-151 85 Sweden
II-6	State of nationality	SE
II-7	State of residence	SE
II-8	Telephone No.	+44 1625 230148
II-9	Facsimile No.	+44 1625 510752

PCT REQUEST

100378/WO

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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 W1Y 6LN 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)	BOYD, Scott
III-2-5	Address:	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)	CAULKETT, Peter, William, Rodney
III-3-5	Address:	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)	HARGREAVES, Rodney, Brian
III-4-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	BOWKER, Suzanne, Saxon
III-5-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-5-6	State of nationality	GB
III-5-7	State of residence	GB

PCT REQUEST

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100378410

III-6	Applicant and/or Inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	JAMES, Roger
III-6-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-6-6	State of nationality	GB
III-6-7	State of residence	GB
III-7	Applicant and/or Inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	JOHNSTONE, Craig
III-7-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-7-6	State of nationality	GB
III-7-7	State of residence	GB
III-8	Applicant and/or Inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	JONES, Clifford, David
III-8-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-8-6	State of nationality	GB
III-8-7	State of residence	GB
III-9	Applicant and/or Inventor	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	MCKERRECHER, Darren
III-9-5	Address:	Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
III-9-6	State of nationality	GB
III-9-7	State of residence	GB
III-10	Applicant and/or Inventor	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	BLOCK, Michael, Howard
III-10-5	Address:	35 Gatehouse Drive Waltham, MA 02451 United States of America
III-10-6	State of nationality	GB
III-10-7	State of residence	US

PCT REQUEST

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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 (LAST, First)	BRYANT, Tracey, et al
IV-1-2	Address:	ASTRAZENECA Global Intellectual Property Mereside Alderley Park Macclesfield, Cheshire SK10 4TG United Kingdom
IV-1-3	Telephone No.	+44 1625 513228
IV-1-4	Facsimile No.	+44 1625 510752
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

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100379/VO

V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	17 August 2001 (17.08.2001)	
VI-1-2	Number	0102764-8	
VI-1-3	Country	SE	
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	141	-
IX-3	Claims	9	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	157	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-13	Priority document(s)	Item(s) VI-1	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	

PCT REQUEST

100378/WO

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X-1	Signature of applicant, agent or common representative	
X-1-1	Name (LAST, First)	BRYANT, Tracey, et al

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	
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PCT (ANNEX - FEE CALCULATION SHEET)

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100379/WO

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only	
0-1	International Application No.	
0-2	Date stamp of the receiving Office	
0-4	Form - PCT/RO/101 (Annex)	
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.92 (updated 01.01.2003)
0-8	Applicant's or agent's file reference	100379/WO
2	Applicant	ASTRAZENECA AB, et al.
12	Calculation of prescribed fees	
		fee amount/multiplier Total amounts (GBP)
12-1	Transmittal fee T	⇒ 55
12-2-1	Search fee S	⇒ 592
12-2-2	International search to be carried out by	EP
12-3	International fee	
	Basic fee (first 30 sheets) b1	278
12-4	Remaining sheets	127
12-5	Additional amount (X)	6
12-6	Total additional amount b2	762
12-7	b1 + b2 = B	1,040
12-8	Designation fees	
	Number of designations contained in international application	94
12-9	Number of designation fees payable (maximum 5)	5
12-10	Amount of designation fee (X)	60
12-11	Total designation fees D	300
12-12	PCT-EASY fee reduction R	-86
12-13	Total international fee (B+D-R) I	⇒ 1,254
12-17	TOTAL FEES PAYABLE (T+S+H+P)	⇒ 1,901
12-19	Mode of payment	cheque
12-20	Deposit account instructions	
	The receiving Office:	United Kingdom Patent Office (RO/GB)
12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	D02934
12-22	Date	14 August 2002 (14.08.2002)

PCT (ANNEX - FEE CALCULATION SHEET)

100378/WO

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12-23	Name and signature	
-------	--------------------	--

VALIDATION LOG AND REMARKS

13-2-3	Validation messages Names	Yellow Applicant 1.:City missing
13-2-4	Validation messages Priority	Yellow! Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Fees	Green? Please confirm that fee schedule utilized is the latest available

PCT

1/1

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100378/VO

PCT-EASY INFORMATION SHEET

(For applicant use only, DO NOT submit this sheet with the international application)

VALIDATION LOG

Yellow	Names Applicant 1.:City missing
Yellow!	Priority Priority 1: The twelve-month time limit for claiming priority would appear to have expired. Please verify.
Green?	Contents The international application contains no drawings. Please verify.
Green?	Fees Please confirm that fee schedule utilized is the latest available

Before submitting the International Application, please carefully verify that:

- the information contained on printed Request form is correct;
- Box X of the Request form has been signed;
- all elements of the international application as indicated in Boxes VII and IX of the Request form have been attached; and,
- the diskette containing the PCT-EASY zip file of the international Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.

ATTENTION

DO NOT modify any indications on the Request form printout. The electronic version of the PCT-EASY application has been locked. If an error or an omission is discovered at this time, you must reopen the stored form for submission, perform necessary amendments and immediately resubmit the form. Finally, a NEW submission diskette must be created manually by resending the corrected stored form to the diskette. The previously created printout and submission diskette must be destroyed in order to prevent the possibility of erroneously sending it to the RO.

A B S T R A C T

COMPOUNDS

The invention relates to the use of a compound of Formula (I) or a salt, solvate or prodrug thereof, wherein $R_{1?}$, $R_{2?}$, $R_{3?}$, n and m are as described in the specification, in the preparation of a medicament for the treatment or prevention of a disease condition mediated through glucokinase (GLK), such as type 2 diabetes.

(A chemical formula should be inserted here - please see paper copy enclosed herewith)

Formula (I)

The invention also relates to a novel group of compounds of Formula (I) and to methods for preparing compounds of Formula (I).



CONSULADO GENERAL DE COLOMBIA

3RD FLOOR, 15-19 GREAT TITCHFIELD STREET, LONDON W1P 7FB
TELEPHONE 020-7637 8883 • TELEFAX 020-7637 5804
E-MAIL consulco@consulco.demon.co.uk

223
X
A

El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este Despacho,

CERTIFICA

Que, **J.B. HODGSON**, Notario Público de Macclesfield, Cheshire, Inglaterra, legalizó la firma del documento precedente y su firma se encuentra certificada por **J. GARBRAH**, Oficial de del Ministerio de Relaciones Exteriores Británico, firma que se encuentra registrada en este Consulado General.

Que, **AntraZeneca AB**, es una Sociedad constituida, organizada y existente en Sodertalje, Suecia, y que cumple con su objeto social de acuerdo con las leyes de ese país.

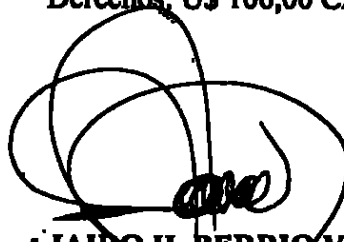
Que, **DAVID ERIC GILES**, en su calidad de Representante Legal de la mencionada Sociedad, debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por **J.B. HODGSON**, Notario Público de Macclesfield, Cheshire, Inglaterra, Gran Bretaña.

El Cónsul General no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los quince (15) días del mes de Noviembre de dos mil (2000).

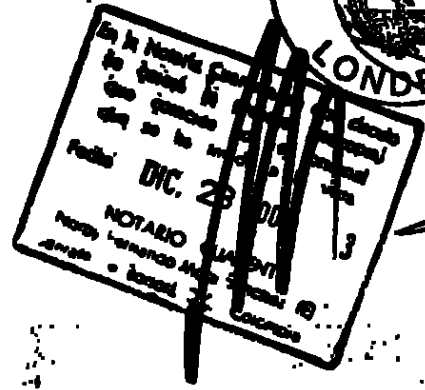
Certificación No.11 /1722

Derechos: US 106,00 CANCELADOS


JAIR H. BERRIO VILLARREAL
Cónsul General

HUGO NAVARRO ALVARADO
TRADUCTOR E INTERPRETE OFICIAL
Reg. 1876 Ministerio 1989

MINISTERIO DE RELACIONES
EXTERIORES
481834
HUGO NAVARRO ALVARADO



SE ASUME
RESPONSABILIDAD DEL TEXTO
2000 NOV 29 A 10:32
DELEGACIONES
SANTAFE DE BOGOTA D.C.

BRIGARD & CASTRO

SANTAFE DE BOGOTA - COLOMBIA

PODER

Yo (nosotros) ASTRAZENECA AB

Domiciliado(s) en: S-151 85, Sodertälje,
SUECIA

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistír 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 creyeran 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 desistír, transigir, comprometer y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 18-58 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

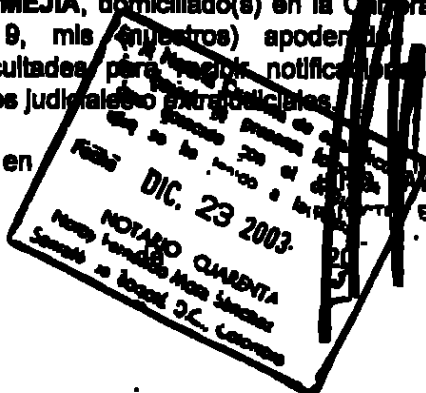
hoy

de

Firma

Nombre

Cargo



POWER OF ATTORNEY

I (We) ASTRAZENECA AB

Domiciled in: S-151 85, Sodertälje
SWEDEN

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de 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 vegetable 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 exploitation 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 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 kinds 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 HECTOR GOMEZ MEJIA, domiciled in Carrera 7 No. 18-58, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in

This

10 NOV 2000 day

of

20

Signature

Name

Title

David Eric Giles

DAVID ERIC GILES
DIRECTOR IP SERVICES

MACCLESFIELD, CHESHIRE
ENGLAND

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 ASTRAZENECA AB

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 ANTE CONSUL COLOMBIANO
ES REQUERIDA**

NOTARIAL CERTIFICATE (CORPORATION)

On this 10 day of November of 2000
Personally appeared before me

DAVID ERIC GILES
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

DIRECTOR IP SERVICES

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 the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of SWEDEN
under date of 3RD JANUARY 2000

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

**NOTARIAL CERTIFICATE
NATURAL PERSON**

de day of of
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 BEFORE COLOMBIAN CONSUL
IS REQUIRED**

226
226

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. **D644894**

Date **14 November, 2000**

This document bears
the signature / seal of **J B Hodgson**

H1120 "ALVAREZ"
IRADU INTERPRETE OFFICER
Em. ad/o Ministerio 1888

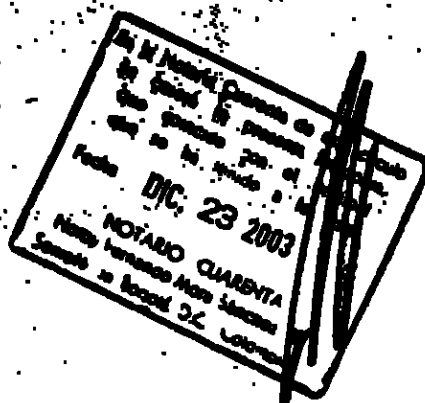
Acting in the capacity of **Notary Public**

Signed by: **J. Garbrah**



J. Garbrah

*For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs*



222
FZ

TRADUCCION OFICIAL No. 432/2000 de las legalizaciones que se encuentran a continuación de un Poder otorgado **ASTRAZENECA AB**, una compañía domiciliada en **S-151 85, Sodertalje, SUECIA** al doctor **RAMIRO CASTRO** y **HECTOR GOMEZ**, **Santafé de Bogotá, D.C., Colombia**, del Inglés al español, las cuales para su identificación se sella con el Sello del Traductor al mismo tiempo que la presente.-

++++
ANEXOS: El Poder arriba mencionado, Certificación Notarial, Certificación por el Secretario de Estado Principal de Su Majestad Para los Asuntos de la Comunidad y el Extranjero en Londres, Inglaterra, Certificación del Consulado General de Colombia en Londres, Inglaterra, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

++++

Firma ilegible (Firmado)

Notario Público

BELLO NOTARIAL EN RELIEVE.

++++

REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

No. D644894

Fecha...14 de Noviembre del año 2000.....

Este documento porta

la firma/sello de J. B. Hodgson

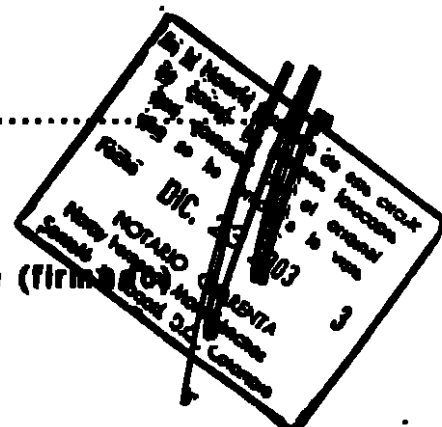
.....
actuando en la capacidad de

Notario Público

.....
Firmado por: J. Garbrah

Firma ilegible (Firmado)

HUGO NAVARRO ALVAREZ
TRADUCTOR E INTERPRETE OFICIAL
Rev. 1876 Minjusticia 1983



238
LZ

Por el Secretario de Estado Principal de
Su Majestad para los Asuntos de la
Comunidad y el Extranjero.

SELLO EN RELIEVE.

**HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.**

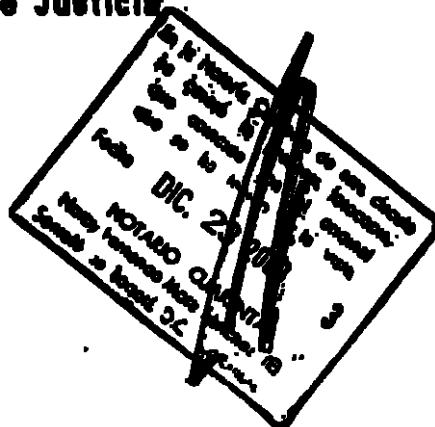
+++++
**EN ESPAÑOL: La Certificación del Consulado General de Colombia
en Londres, Inglaterra bajo el Número de Certificación 11/1722 de
fecha 15 de Noviembre del año 2000; Autenticación Hasta por el
Ministerio de Relaciones Exteriores de Colombia bajo el Número
481834 de fecha 29 de Noviembre del año 2000.**

(Pagados Derechos por valor de \$106.00 Dólares)

+++++
**ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS
ADJUNTOS.**


HUGO NAVARRO ALVAREZ
TRADUCTOR E. INTERPRETE OFICIAL
Res. 1876 Minjusticia 1993

**Resolución Número 1876 del Ministerio de Justicia
Fecha: 4 de Diciembre del año 2000.**



REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Firma Responsable:



Fecha:



281
280

2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado
Aztrazeneca AB

Oficio N° 05195

ASUNTO:	Radicación N°	04 022003
	Solicitud internacional	PCT/GB02/03745
	Fecha inicio fase nacional	17/03/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPÉDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 31 MAYO 2004.