

PETITORIO

AS: 106.345



FORMULARIO ÚNICO DE ENTRADA EN F

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-025246-00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-022003-00007-0000

Fecha: 2008-03-10 16:51:56 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 329 CTOINFORMACION Folios: 281

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SOLICITUD DE:

☒ Patente de Invención.

☐ Capítulo I.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-022003-A-00000-0000

Fecha: 2004-03-10 17:16:23 Dep. 2020 DIR.NUEVASOR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 279

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5 PCT (86)

Solicitud Internacional No. PCT/GB2002/03745
Publicación Internacional No. WO 2003/015774 A1

Fecha 15-08-2002
Fecha 27-02-2003

6 Título (54): COMPUESTOS QUE AFECTAN LA GLUCOCINASA

7 Clasificación Internacional (51):

8 Prioridad

SI ☒ NO ☐

(33) País de Origen

SE

(32) Fecha

17-08-2001

(31) Número de Solicitud

0102764-8

ESTA ES UNA

EXPEDIENTE

SOLICITUD

No. 04-022.003

DIVISIONAL O FRACCIONADA DEL

9 Comprobante de pago No. 08-15,951

Fecha 07-03-2008

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

- 128
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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, benztiázida);
 - 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.

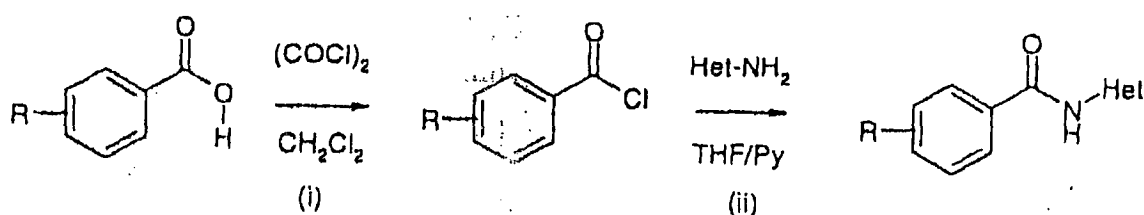
La condensación de un ácido con una amina heterocíclica (Ruta 1) se

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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).

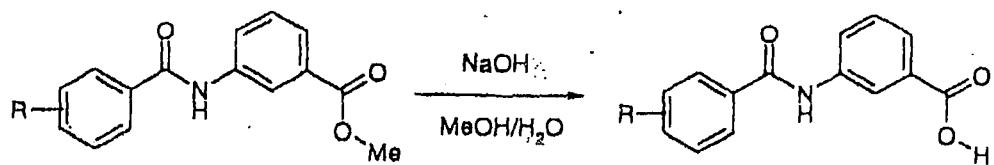
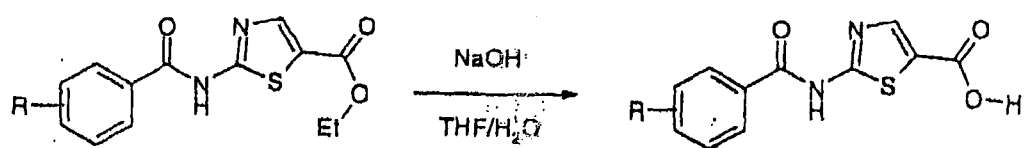
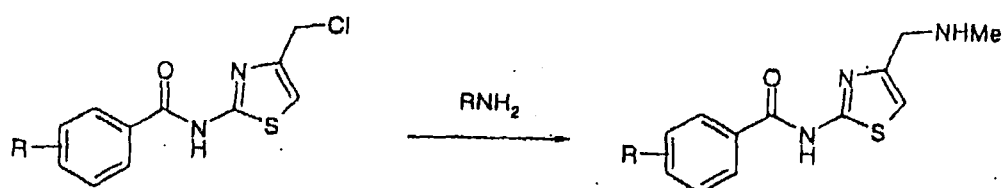
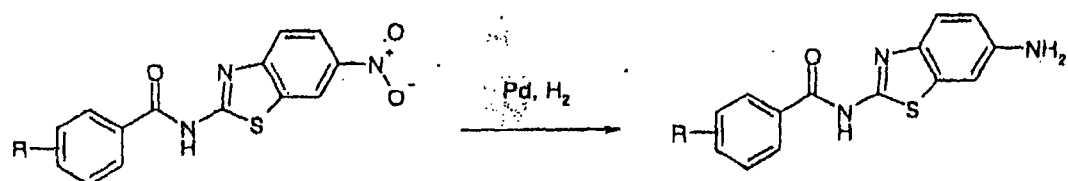
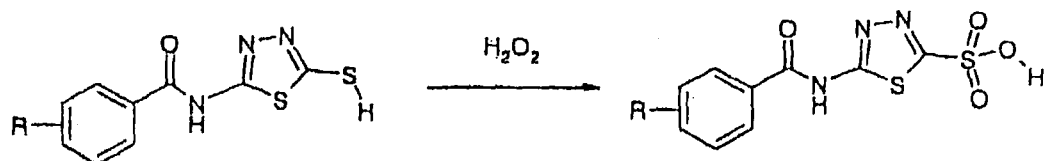
Las rutas preparativas restantes (Rutas 2-18) comprenden la manipulación adicional del compuesto con un enlace de amida en su lugar. Otras rutas preparativas se resumen en las Rutas 19-29. Ejemplos de rutas 1-29 se proveen en los ejemplos siguientes. Los reactivos y condiciones dados son únicamente para ilustración y, generalmente, pueden emplearse métodos alternativos.

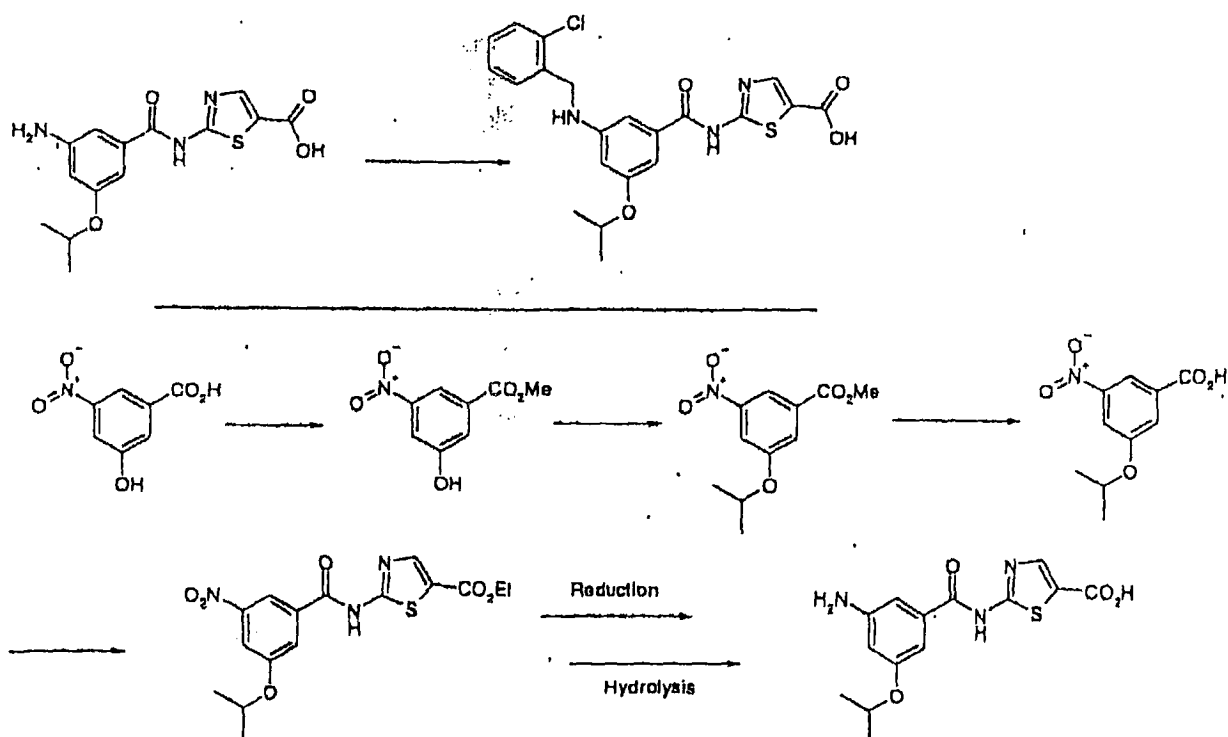
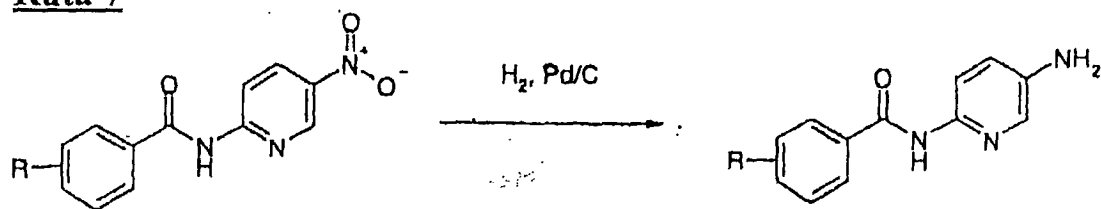
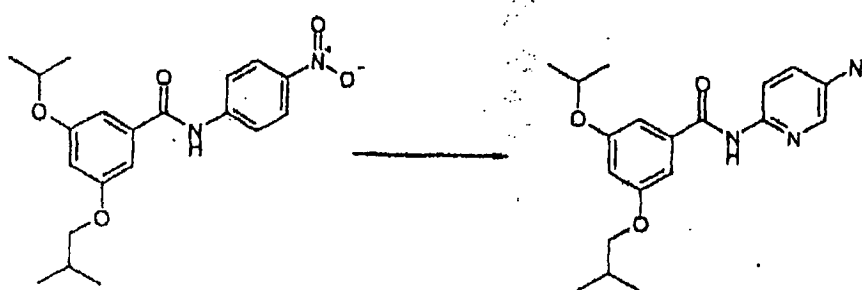
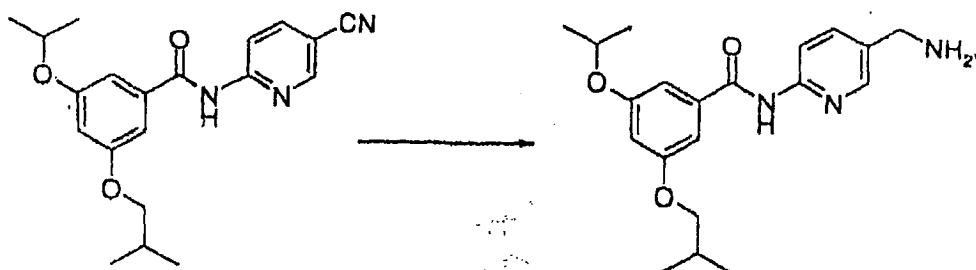
Ruta 1



Otras reacciones formadoras de amida comprenden:

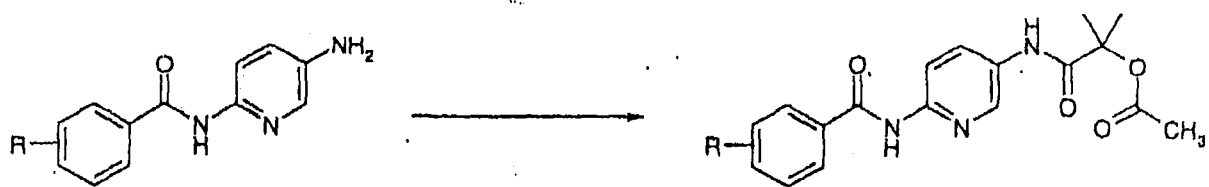
- 1a: Cloruro de oxalilo en la presencia de un solvente o base adecuados;
- 1b: Reactivos de acoplamiento tales como HATU o EDAC en la presencia de un solvente o base adecuados; y
- 1c: POC13/Piridina, de acuerdo con Dirk T.S. Rijkvers, Hans P.H.M. Adams, H. Coenraad Hemquer, Godefridus I. Tesser; Tetrahedron, 1995, 51(41), páginas 11235-11250.

Ruta 2a y 2b**Ruta 3****Ruta 4****Ruta 5**

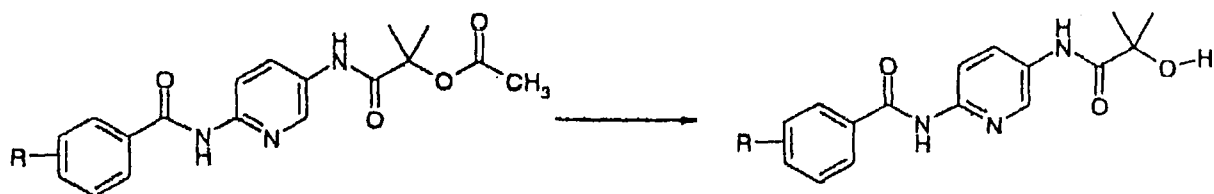
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150**Ruta 6****Ruta 7****Ruta 7b:****Ruta 7c:**

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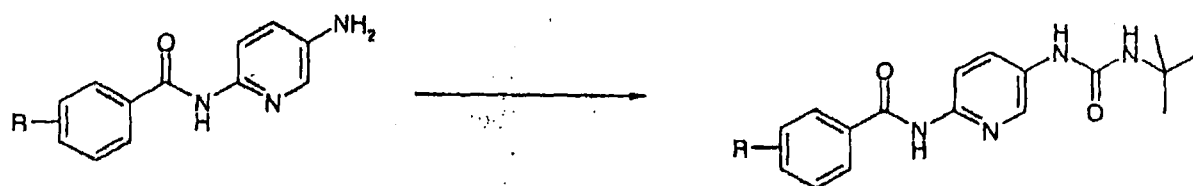
Ruta 8



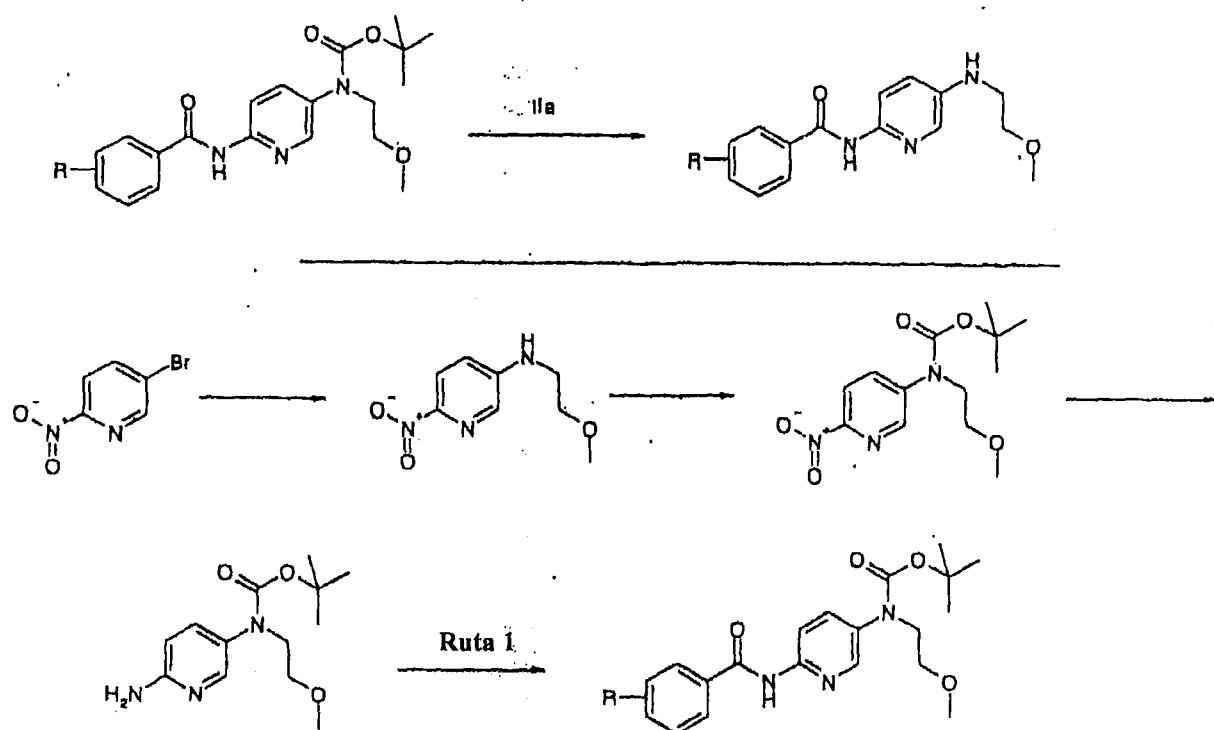
Ruta 9



Ruta 10

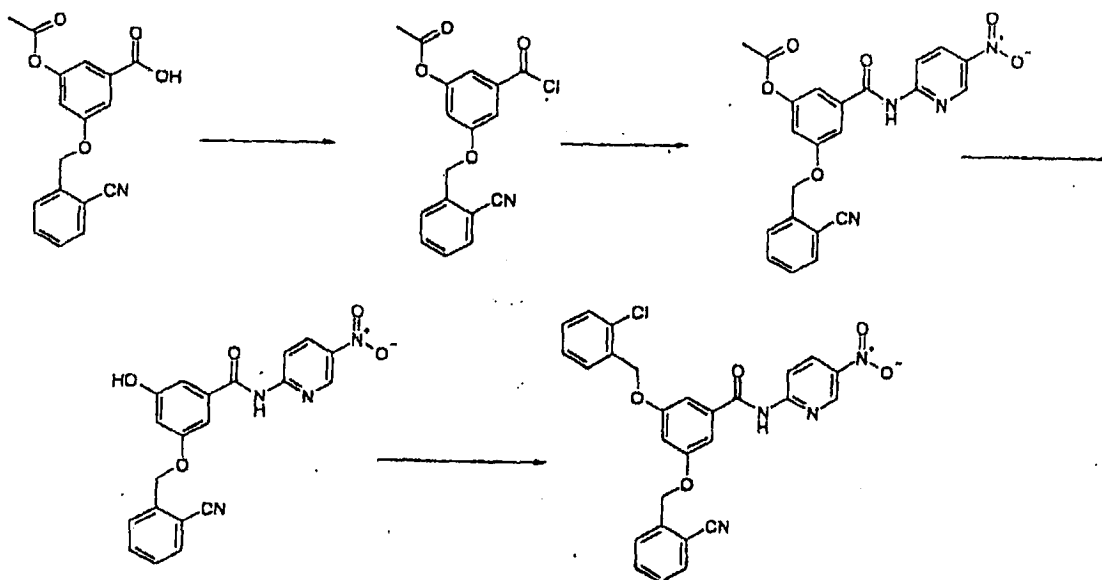
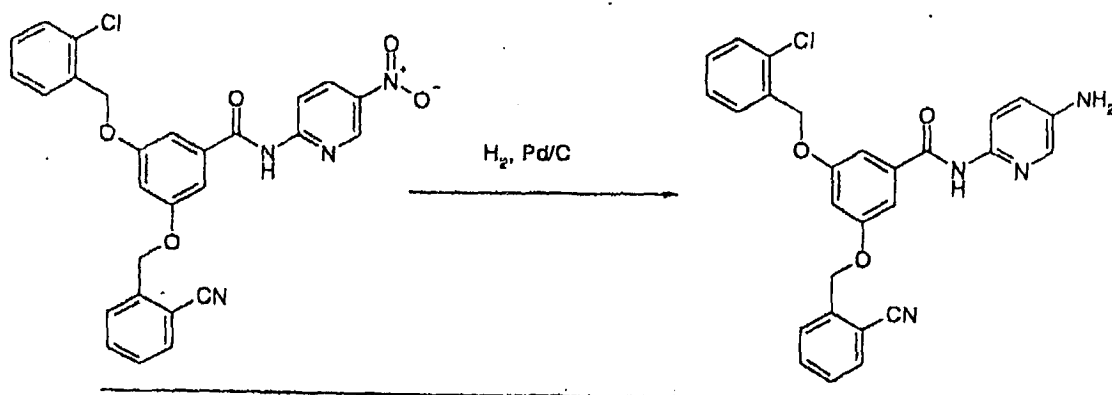


Ruta 11

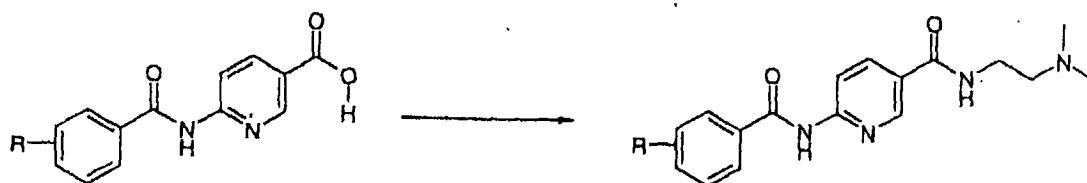


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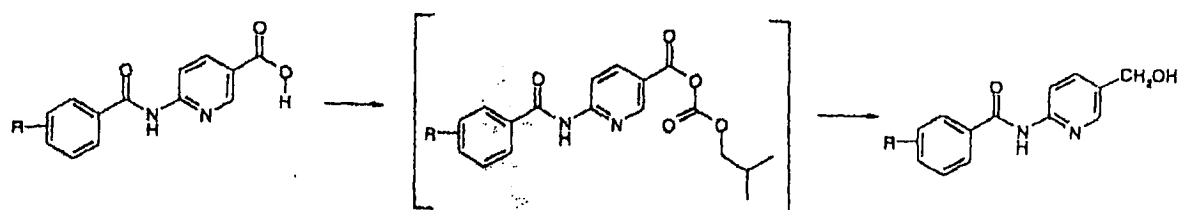
Ruta 12

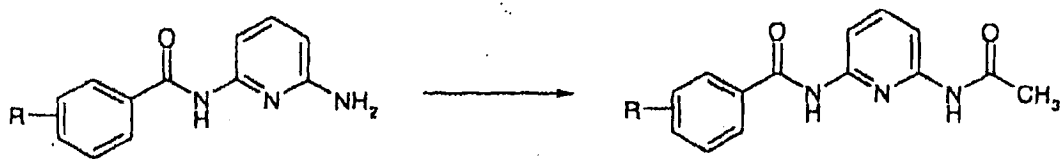
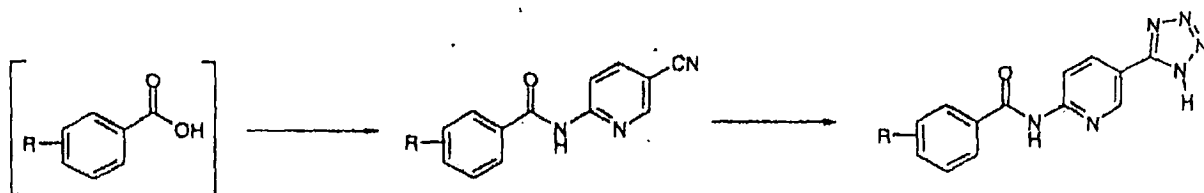
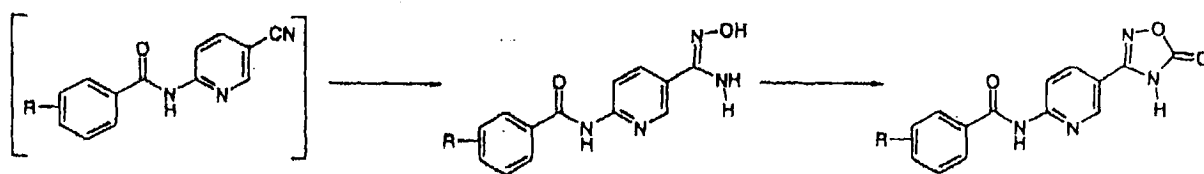
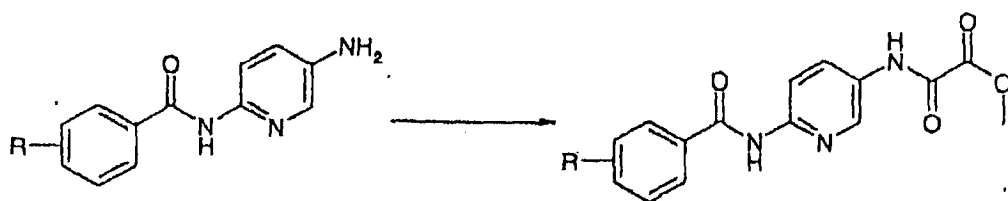
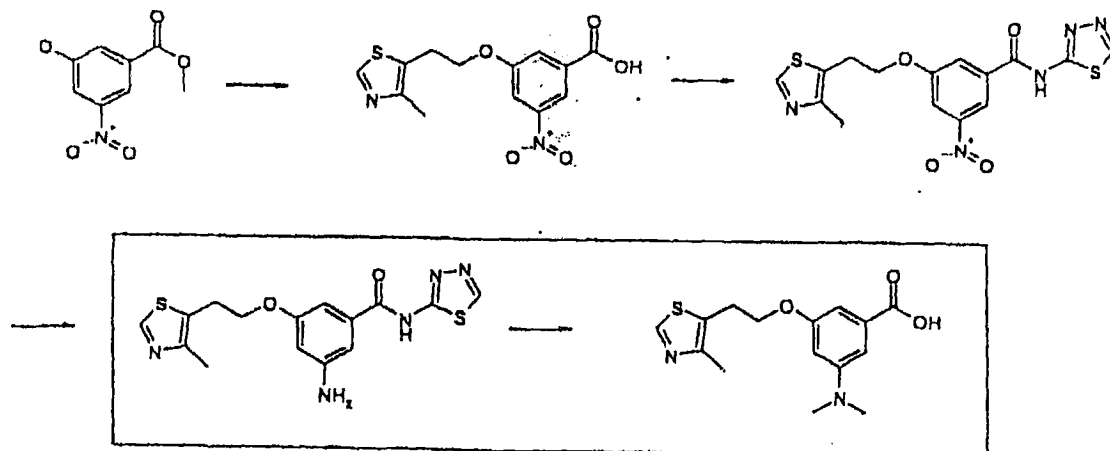


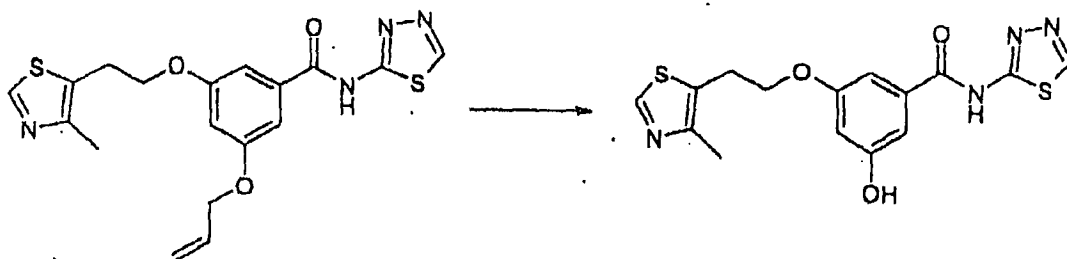
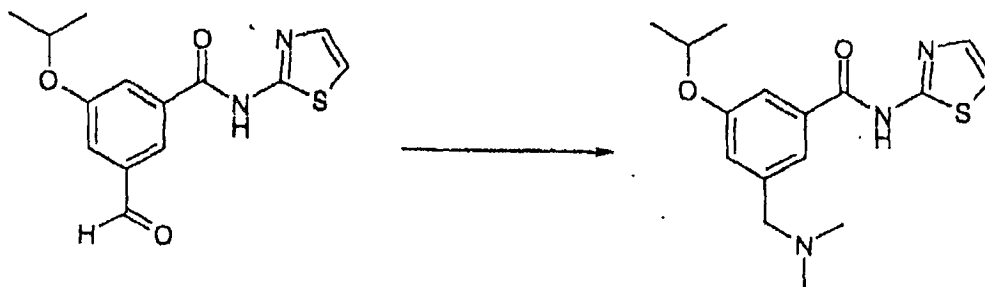
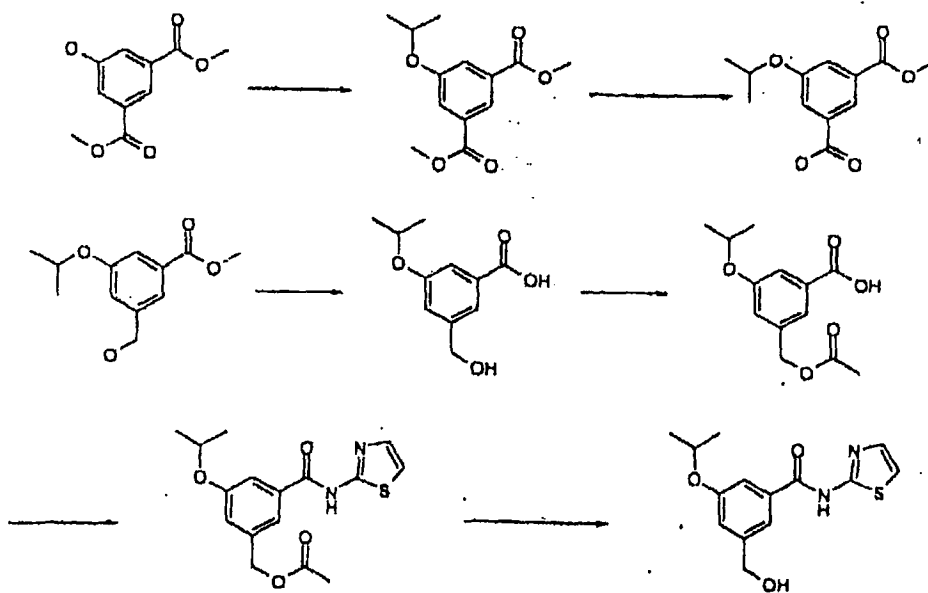
Ruta 13

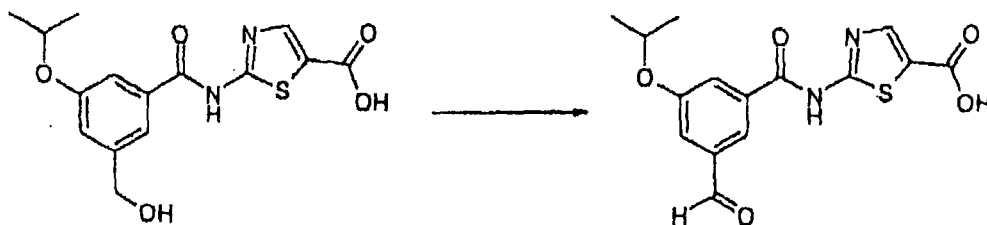
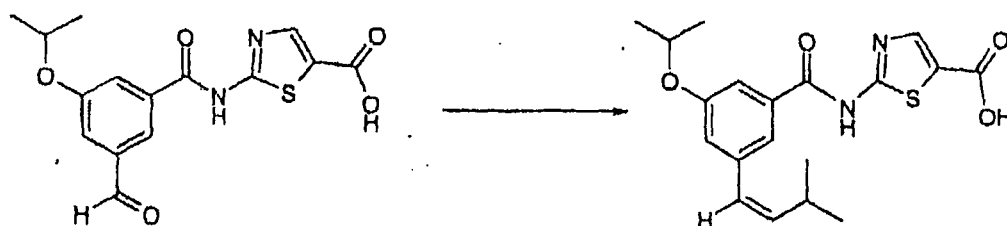
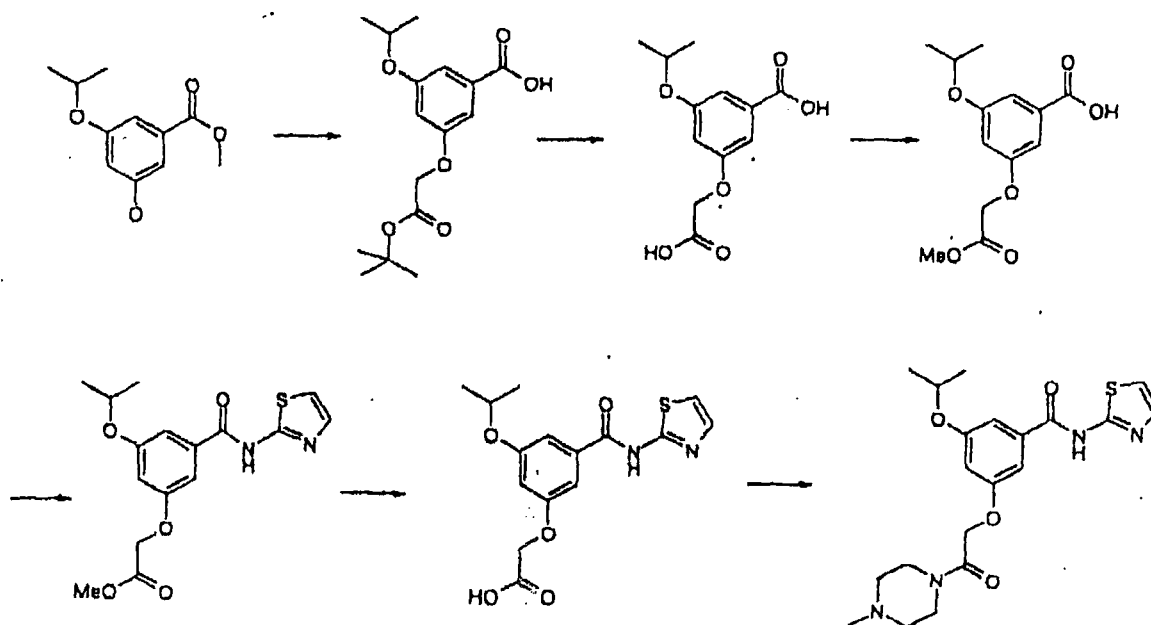
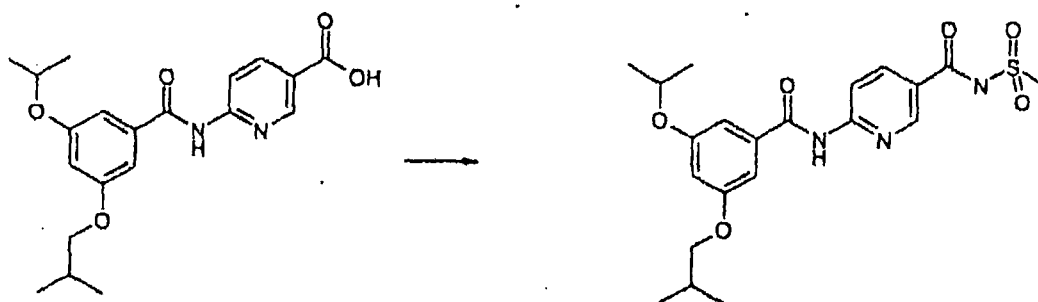


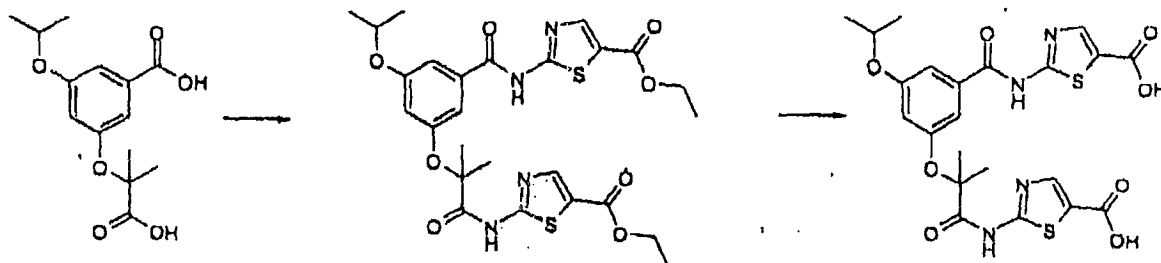
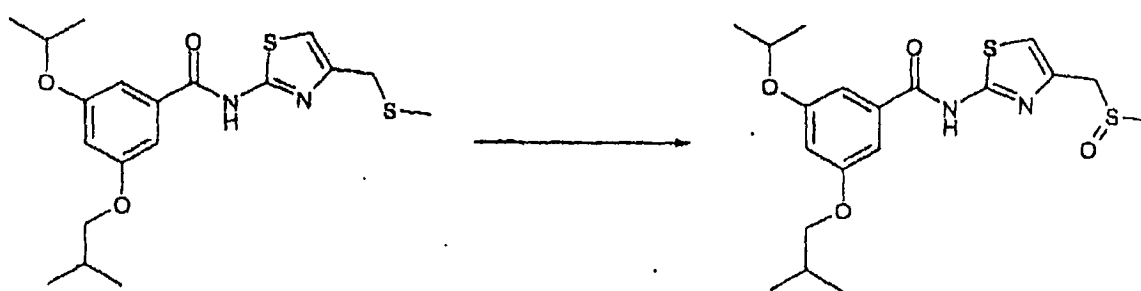
Ruta 14



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+33**Ruta 15****Ruta 16****Ruta 17****Ruta 18****Ruta 19:**

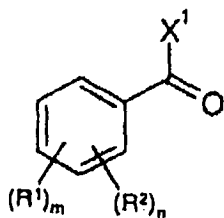
135
134**Ruta 20:****Ruta 21:****Ruta 22:****Ruta 23:**

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135**Ruta 24:****Ruta 25:****Ruta 26:****Ruta 27:**

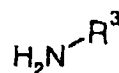
13A
+ 26**Ruta 28:****Ruta 29:**

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),



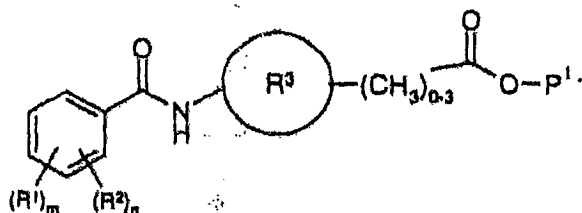
Fórmula (IIIa)



Fórmula (IIIb); o

en donde X^1 es un grupo saliente

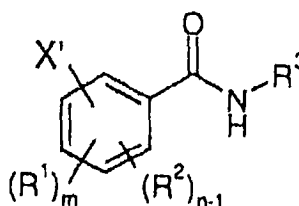
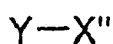
- (b) para compuestos de Fórmula (I) en donde R^3 se sustituye con $-(CH_2)_{0-3}COOH$, desprotección de un compuesto de Fórmula (IIIc),

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Fórmula (IIIc)

en donde P^1 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),

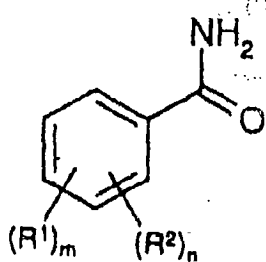


Fórmula (IIIId)

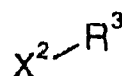
Fórmula (IIIe)

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 X^1 es $-SO-Z-$ o $-SO_2-Z-$, oxidación del correspondiente compuesto de Fórmula (I) en donde X o X^1 respectivamente es $-S-Z-$;
- (e) reacción de un compuesto de Fórmula (IIIf) con un compuesto de Fórmula (IIIg),



Fórmula (IIIf)



Fórmula (IIIg); 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.

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 L^2-Z- en donde L^2 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 $N(R^6)-Z-$, X' es un grupo de Fórmula $H-(R^6)N-Z-$ y X'' es un grupo saliente (alternativamente X' es un grupo de Fórmula L^2-Z- en donde L^2 es un grupo saliente y X'' es un grupo o Fórmula $-N(R^6)-H$), 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 $-SO_2N(R^6)-Z-$, X' es un grupo de Fórmula $H-N(R^6)-Z-$ en donde L^2 es un grupo saliente y X'' es un grupo sulfonilo activado tal como un grupo de Fórmula $-SO_2-Cl$, 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 (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 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 (IIIId) y (IIIe) 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 (IIIId) y (IIIe) 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 X^1 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 alcoxicarbonilo inferior (por ejemplo 1-metoxicarboniloietilo, 1-etoxicarboniloietilo); grupos alquilo inferior arilo (por ejemplo *p*-metoxibencilo, *o*-nitrobencilo, *p*-nitrobencilo, benzhidrilo y ftalidilo); grupos tri(alquilo inferior)sililo (por ejemplo trimetilsililo y *t*-butildimetilsililo); grupos alquilo inferior tri(alquilo inferior)sililo (por ejemplo trimetilsililetilo); y grupos (2-6C)alquenilo (por ejemplo alilo y viniletilo).

Métodos particularmente apropiados para el retiro de grupos protectores carboxilo comprenden por ejemplo hidrólisis catalizada por ácido, metal o enzimáticamente.

Ejemplos de grupos protectores hidroxil comprenden grupos alquenilo inferior (por ejemplo alilo); grupos alcanilo inferior (por ejemplo acetilo); grupos alcoxicarbonilo inferior (por ejemplo *t*-butoxicarbonilo); grupos alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos alcoxicarbonilo inferior arilo (por ejemplo benzoiloxicarbonilo, *p*-metoxibenciloxicarbonilo, *o*-nitrobenciloxicarbonilo, *p*-nitrobenciloxicarbonilo); 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 alcoxicarbonilo inferior (por ejemplo *t*-butoxicarbonilo); alqueniloxicarbonilo inferior (por ejemplo aliloxicarbonilo); grupos alcoxicarbonilo inferior (por ejemplo benciloxicarbonilo, *p*-metoxibenciloxicarbonilo, *o*-nitrobenciloxicarbonilo, *p*-nitrobenciloxicarbonilo); trialquilsililo (por ejemplo trimetilsililo y *t*-butildimetilsililo); grupos alquilideno (por ejemplo metilideno); bencilideno y bencilideno sustituido.

Métodos apropiados para el retiro de grupos protectores hidroxil 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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X43

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.

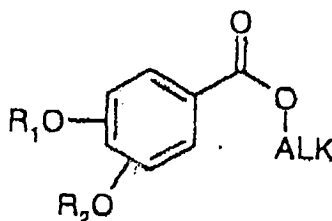
Abreviaturas

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;

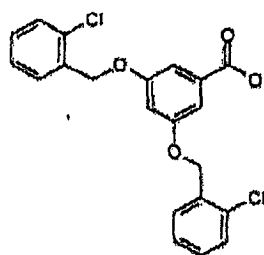
HATU	O-(7-azabenzotriazo-1-il)-N,N,N',N'- tetrametiluronio hexafluorofosfato;
LCMS	cromatografía líquida / espectroscopía de masa;
MPLC	cromatografía líquida de presión media;
RT	temperatura ambiente; y
THF	tetrahidrofurano.

Métodos genéricos para la alquilación de ésteres de mono- y di-hidroxi benzoato:

Los siguientes métodos genéricos de alquilación se mencionan en los Ejemplos que siguen.



Método Genérico A – síntesis de diéteres simétricos ($R_1 = R_2$)



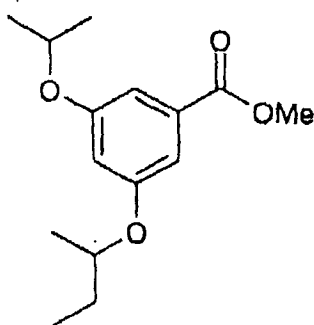
Compuesto (a)

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 ($MgSO_4$), se filtraron, se concentraron *in vacuo* para producir un aceite marrón el cual se trituro con éter dietílico / isohexano para producir compuesto (a) como un sólido blancuzco (195g, 100%); 1H nmr (d_6 -

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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 ($R_1 = R_2$)



Compuesto (b)

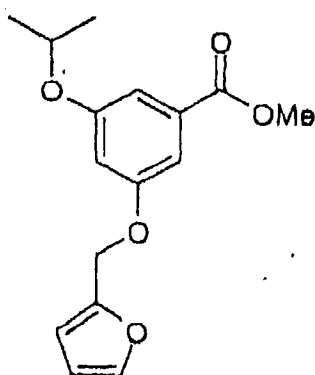
Metil 3,5-dihidroxibenzoato (16.8g, 0.1mol) se disolvió en dimetilformamida (180ml), se agregó carbonato de potasio pulverizado (27.6 g, 0.2mol), seguido por 2-yodopropano (10ml, 0.1mol), y la suspensión resultante se agitó durante la noche a temperatura ambiente bajo una atmósfera de argón. La mezcla 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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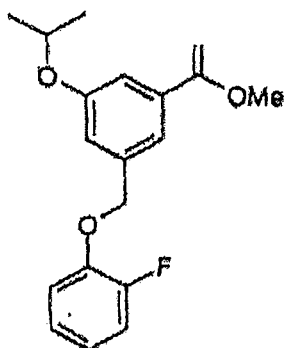
(MgSO₄), se filtró y se concentró *in vacuo* para producir un aceite incoloro el cual se cromatografió (columna de destello en sílice (20g), eluyendo con isohexano que contenía acetato de etilo (5 % v/v) para producir metil 3-(2-butiloxi) 5-isopropiloxi benzoato como un aceite incoloro (1.06g); ¹H nmr (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 isohexano 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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147Método Genérico D - síntesis de diéteres asimétricos:

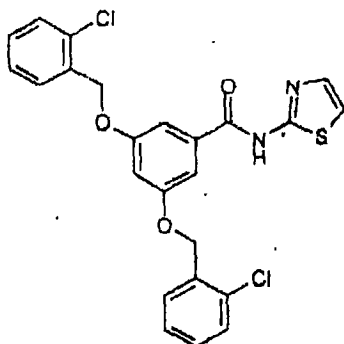
Compuesto (d)

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.

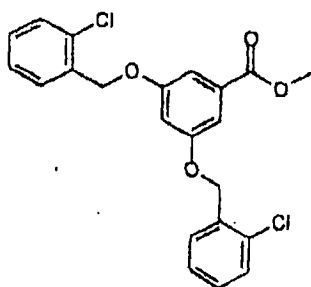
EJEMPLO ARuta 1: 2-[3,5-Di-(2-clorobenciloxi)benzoil]amino]-tiazol

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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:

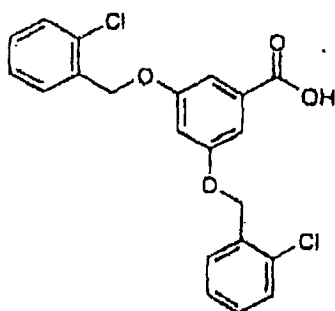


Compuesto (a)

Metil 3,5-dihidroxibenzoato (74.1g, 0.44M) se disolvió en

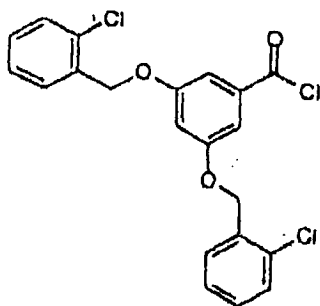
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dimetilformamida (400ml), se agregó carbonato de potasio (152g, 1.10M), se agitó durante 15 minutos, luego se agregó 2-clorobencilcloruro (117ml, 0.92M) y se calentó a 100°C bajo una atmósfera de argón. Después de 3 horas la mezcla de reacción se enfrió 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).



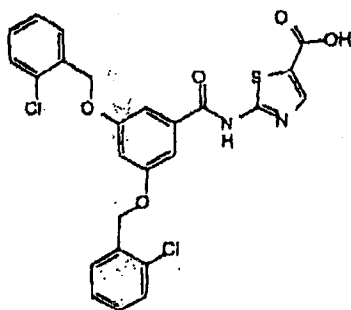
Compuesto (c)

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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 (d_6 -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

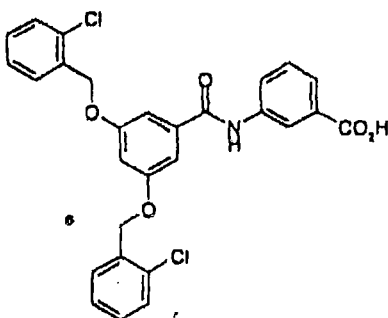


Una solución de 2-[3,5-di-(2-clorobenciloxi)benzoil]aminotiazol-5-carboxilato de etilo (158mg, 0.28 mmol) en THF (2 ml) se trató con solución de hidróxido de sodio (0.57 ml of 2M, 1.4 mmol), y la reacción se agitó a 40 - 50 °C, hasta que se consiguió una hidrólisis completa (con monitoreo de tlc, tiempo 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 (d_6 -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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151**EJEMPLO C**

Ruta 2b: ácido [3,5-di-(2-clorobenciloxi)benzoil]aminobencen-3-carboxílico

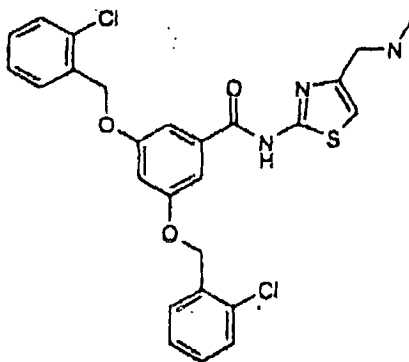


Una suspensión de [3,5-di-(2-clorobenciloxi)benzoil]aminobencen-3-carboxilato de metilo (455mg, 1.04 mmol) en THF se trató con solución de hidróxido de sodio (0.85 ml ó 2M, 1.7 mmol), y la reacción se agitó a temperatura ambiente, con monitoreo de tlc. Se realizaron adiciones de metanol (3 gotas) y otras 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 (d_6 -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

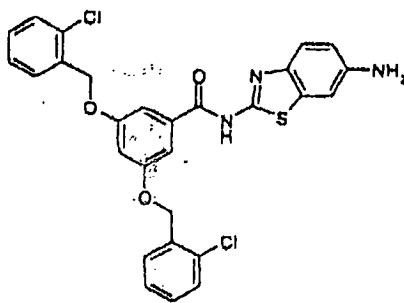
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2-[3,5-Di-(2-clorobenciloxi)benzoyl]amino]-4-clorometiltiazol (56mg, 0.10mM) se disolvió en 33% metilamina en alcohol metilado (4ml) y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró *in vacuo*, se trituro con metanol, se filtró y se secó bajo alto vacío para producir el compuesto del título como un sólido incoloro (30mg, 57%); ^1H nmr (d6-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

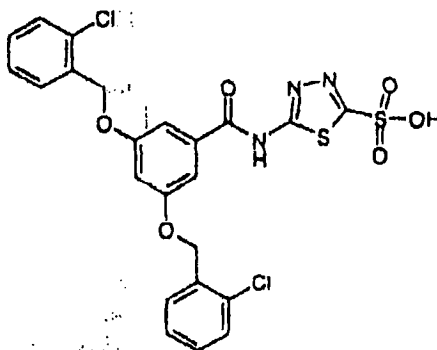
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dimetilformamida (5ml). Se agregó 5% paladio sobre carbono (46mg) bajo una atmósfera de argón, seguidamente la mezcla de reacción se agitó bajo una atmósfera de hidrógeno durante 16 horas. La mezcla de reacción se filtró a través de celita, se concentró *in vacuo*, se trituroó 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)benzoil)amino]-6-nitrobenzotiazol se preparó de 3,5-di-(2-clorobenciloxi) benzoil 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)benzoil)amino]-[1,3,4]tiadiazol-2-sulfónico



5-[3,5-Di-(2-clorobenciloxi)benzoil)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

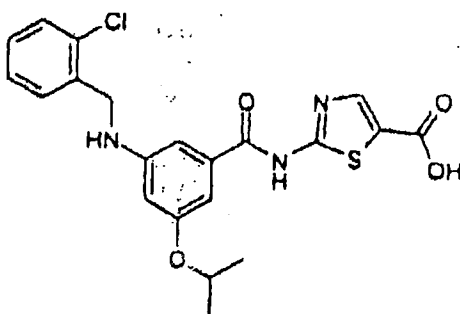
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(1H, m); 7.37 (4H, m); 7.45 (2H, m); 7.50 (2H, m); 7.62 (2H, m). MS (M-H⁺)⁻ 564, 566.

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

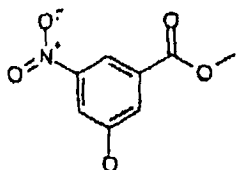
Ruta 6: ácido 2-[(3-isopropoxi-5-(2-clorobencilamino)benzoil)amino]-5-tiazolcarboxílico



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.

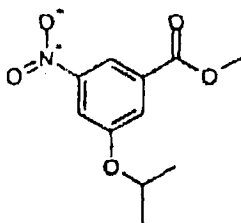
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Ácido 2-[(3-isopropiloxi-5-aminobenzoil)amino]-5-tiazolcarboxílico se preparó como sigue:



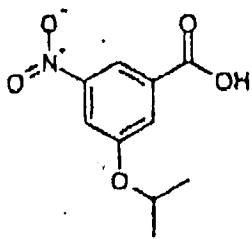
Compuesto (d)

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).



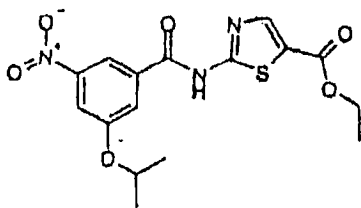
Compuesto (e)

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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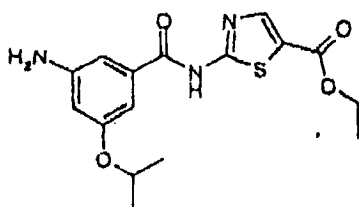
Compuesto (f)

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 (M-H^+) 224.



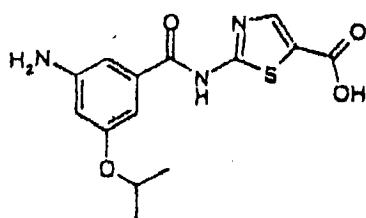
Compuesto (g)

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).

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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).

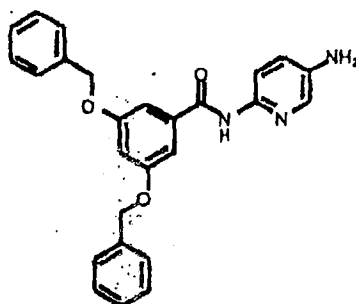


Compuesto (k)

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

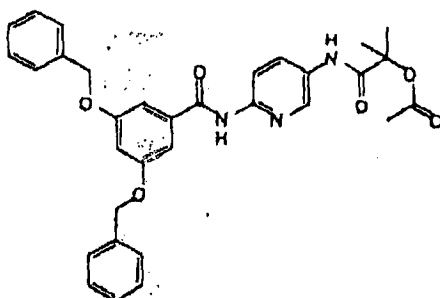


A una solución agitada de 2-[(3,5-dibenzoyloxymethyl)amino]-5-nitropyridina (910 mg) en DMF (6 ml) se agregó polvo de zinc (1300 mg) y una solución hexahidrato de cloruro férrico (1700 mg) en agua (6 ml). La mezcla resultante se agitó a 120°C durante tres horas. Se dejó enfriar a temperatura ambiente. 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-dibenzoyloxymethyl)amino]-3-nitropyridina requerida se preparó por un método análogo al dado en Ejemplo A (ruta 1), a partir de 2-amino-5-nitropyridina; 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-dibenzoyloxymethyl]amino}-piridin-3-il}-2-acetoxi-2-metil-propionamida

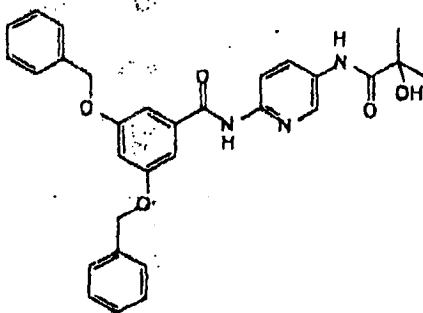


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A una solución agitada de 2-[(3,5-dibenciloxibenzoil)amino]-5-aminopiridina (200 mg) en THF (2 ml) y piridina (2 ml) se agregó una solución de cloruro de 2-acetoxiisobutirilo (98 mg) en THF (1 ml). La mezcla se agitó a temperatura ambiente durante 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 MgSO_4 . 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, $^1\text{H NMR } \delta$ (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)⁻.

EJEMPLO J

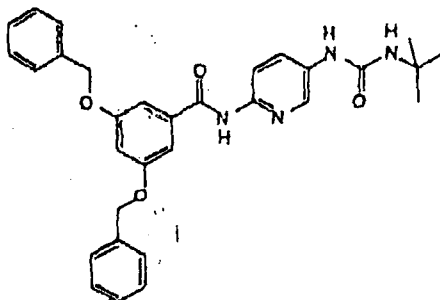
Ruta 9: N-{6-[(3,5-dibenciloxibenzoil)amino]-piridin-3-il}-2-hidroxi-2-metil-propionamida



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 $\text{LiOH}\cdot\text{H}_2\text{O}$ (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, $^1\text{H NMR } \delta$ (d_6 -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)⁺.

EJEMPLO K

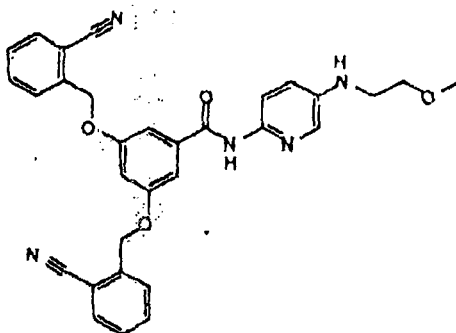
Ruta 10: 3,5-dibenciloxi-N-(5-(((*tert*-butilamino)carbonil)amino)piridin-2-il)benzamida



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 (d_6 -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



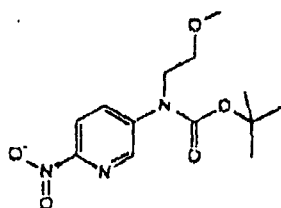
A una solución agitada de *tert*-butil 6-({3,5-di(2-cianobenciloxi)benzoil)amino}piridin-3-il(2-metoxietil)carbamato (237 mg) en diclorometano (10 ml) se agregó ácido trifluoroacético (3 ml). La solución se agitó a temperatura ambiente durante tres horas. El material volátil se retiró por

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100

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:

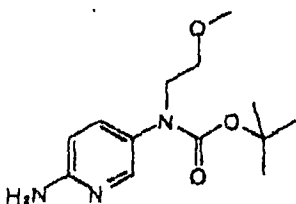
Preparación de *tert*-butil 2-nitropiridin-5-il(2-metoxietil)carbamato



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(difenilfosfino)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)⁺.

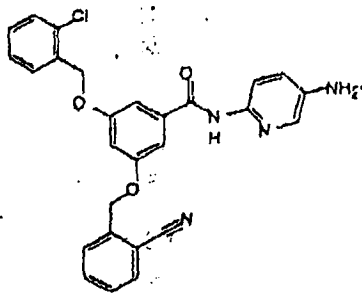
Preparación de *tert*-butil 2-aminopiridin-5-il(2-metoxietil)carbamato



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

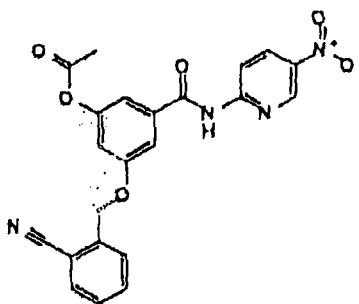
Ruta 12: *N*-(5-aminopiridin-2-il)-3-[(2-clorobencil)oxi]-5-[(2-cianobencil)oxi]benzamida



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.

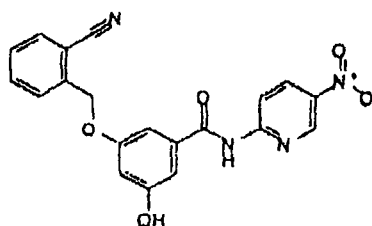
Los materiales iniciales requeridos se prepararon como sigue:

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

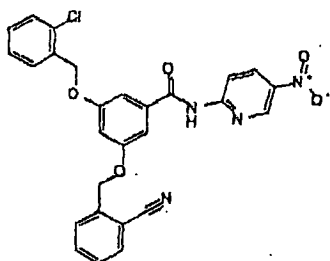


Una suspensión de 3-[[[(5-nitropiridin-2-il)amino]carbonil]-5-[(2-cianobencil)oxi]fenil acetato (5710 mg) en THF (35 ml) se trató con 25% NaOMe en metanol (6 ml). Se agitó a temperatura ambiente durante 30

165
164

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 MgSO_4 . 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 $\text{rt} = 2.38$ min (90.5%). $\text{ES}^+ 391.45 (\text{M}+\text{H})^+$.

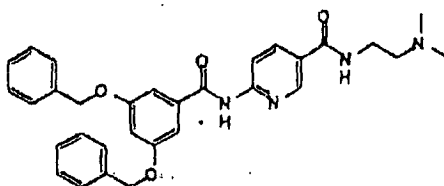
Preparación de N-(5-nitropiridin-2-il)-3-[(2-clorobencil)oxi]-5-[(2-cianobencil)oxi]benzamida



Una solución de N-(5-nitropiridin-2-il)-3-[(2-cianobencil)oxi]-5-hidroxibenzamida (195 mg) en DMF (3 ml) se trató con Ag_2CO_3 (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 MgSO_4 . 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, $^1\text{H NMR } \delta (\text{d}_6\text{-DMSO})$: 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 $\text{rt} = 3.27$ min (97.4%), $\text{ES}^+ 515.50 (\text{M}+\text{H})^+$

EJEMPLO N

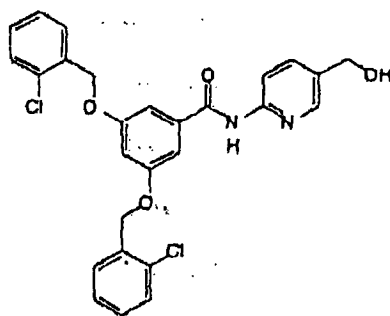
Ruta 13: 6-[[3,5-Di-(benciloxi)benzoil]amino]-N-[2-(dimetilamino)etil]nicotinamida



Diisopropyletilamina (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

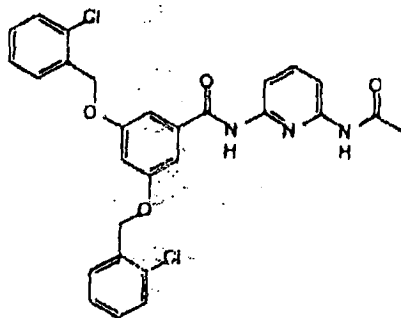


A una solución fría (-15 °C) de ácido 2-[3,5-di-(2-clorobenciloxi)benzoil]amino]-piridin-5-carboxílico (305 mg, 0.59 mmol) en dimetoxi etano (5ml) se agregó 4-metil)morfolina (80μl, 1eq) e isobutil cloroformato (76μl, 1.02 eq). La mezcla de reacción se agitó a -15 °C durante 15 minutos y luego se filtró; el residuo se lavó con dimetoxi etano

(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 (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%), $\text{ES}^+ 509 (\text{M}+\text{H})^+$.

EJEMPLO P

Ruta 15: N-{6-[3,5-di-(2-clorobenciloxibencil)amino]-piridin-2-il}-2-acetamida

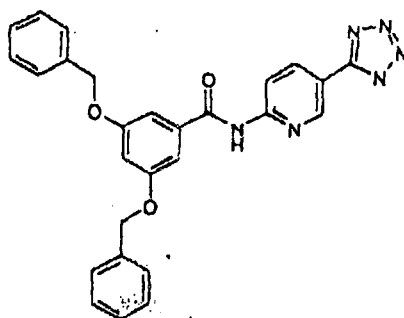


A una solución de 2-[(3,5-di-(2-clorobenciloxibenzoyl)amino]-6-aminopiridina (220 mg, 0.45 mmol) en tetrahydrofurano (4 ml) se agregó piridina (43 mg, 0.54 mmol) y cloruro de acetilo (42 mg, 0.54 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se 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); $\text{ES}^+ 536/538 (\text{M}+\text{H})^+$.

El material inicial, 2-[(3,5-di-(2-clorobenciloxibenzoil)amino]-6-aminopiridina, se ejemplifica aquí como Ejemplo número 106.

EJEMPLO Q

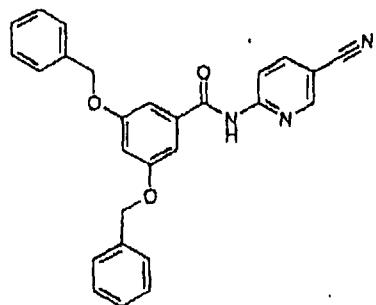
Ruta 16: 3,5-bis(benciloxi)-N-[5-(1H-tetraazol-5-il)piridin-2-il]benzamida



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

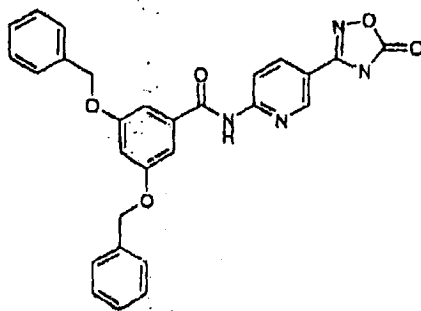


El compuesto del título se preparó como se describe en Ejemplo A (ruta 1), a partir de 2-amino-5-cianopiridina y 3,5-bis(benciloxi) benzoil cloruro, ^1H NMR δ (d_6 -DMSO): 5.19 (4H, s); 6.89 (1H, m); 7.26-7.46 (12H, m); 8.27 (1H, dd), 8.33 (1H, d); 8.84 (1H, s); 11.23 (1H, br s); m/z (LCMS; ESI+) 436 (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

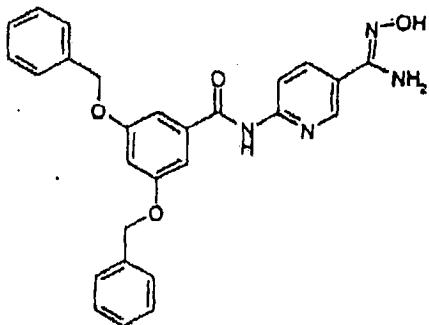
Ruta 17; 3,5-bis(benciloxi)-N-[5-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)piridin-2-il]benzamida



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^+).

El material inicial requerido se preparó como sigue:

Preparación de 3,5-bis(benciloxi)-N-{5-[(hidroxiamino)(imino)metil]piridin-2-il}benzamida

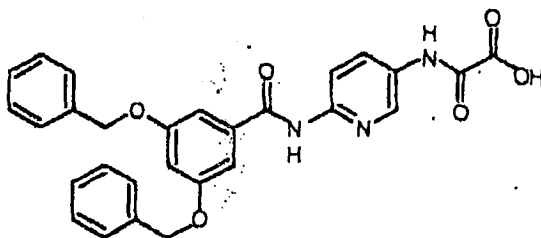


Una mezcla de 3,5-bis(benciloxi)-N-(5-cianopiridin-2-il)benzamida (212 mg, 0.49 mmol), trietilamina (170 μ L, 1.22 mmol) e hidroxilamina clorhidrato (85 mg, 1.22 mmol) en etanol (5 mL) se calentó a reflujo durante la noche. La mezcla se enfrió y se concentró bajo presión reducida. El residuo se purificó 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

171 170

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 (3 mL) 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 (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); m/z (LCMS; ESI+) 498 (MH^+).

El material inicial requerido se preparó de acuerdo con Ejemplo H (ruta 7).

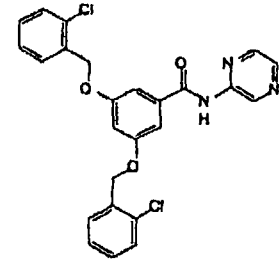
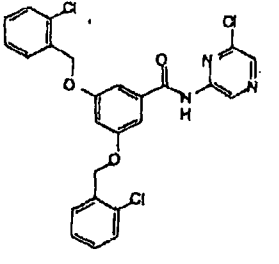
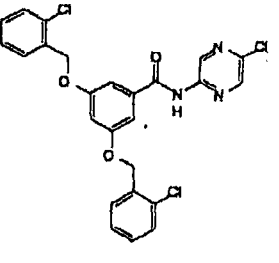
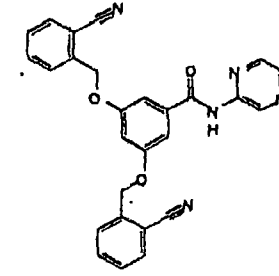
EJEMPLO T:

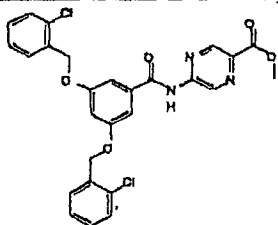
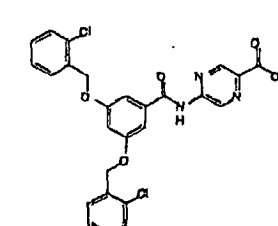
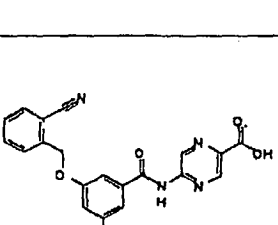
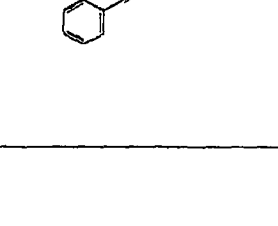
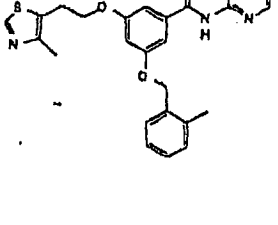
Por métodos análogos a los descritos más arriba se elaboraron además los siguientes compuestos, Ejemplos número T_1 a T_{20} .

Compuesto T_9 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

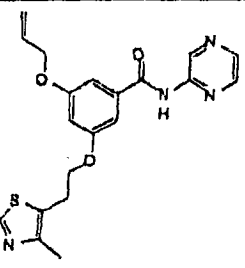
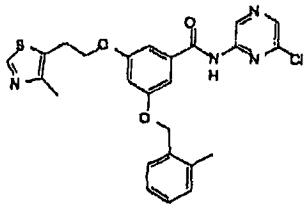
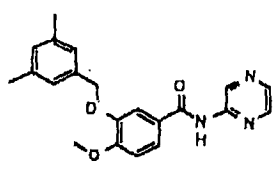
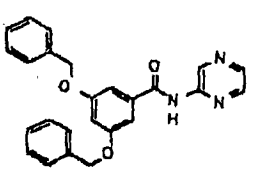
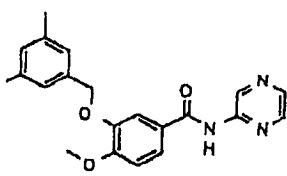
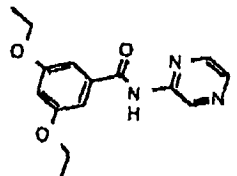
172
H

(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.

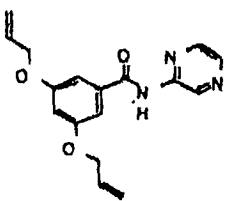
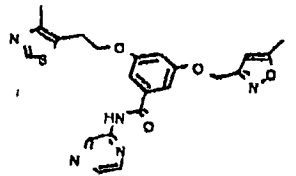
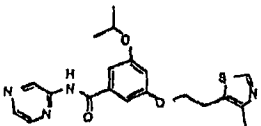
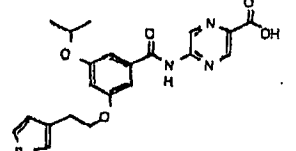
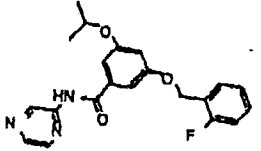
Ejemplo	Estructura	Ruta	NMR
1		1	1H NMR d (d6-DMSO): 5.26 (4H, s); 6.96 (1H, m); 7.38-7.45 (6H, m); 7.53 (2H, m); 7.62 (2H, m); 8.43 (1H, d); 8.49 (1H, m); 9.42 (1H, m); 11.13 (1H, s).
2		1	1H NMR d (d6-DMSO): 5.25 (4H, s); 6.97 (1H, m); 7.38-7.45 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 8.64 (1H, d); 9.26 (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).
4		1	1H 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	1H NMR d (d6-DMSO): 3.90 (3H, s); 5.24 (4H, s); 6.97 (1H, m); 7.39 (6H, m); 7.50

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

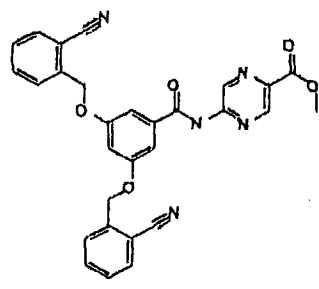
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175

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		

175
174

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:



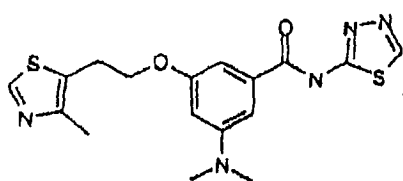
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^1H NMR δ (d_6 -DMSO): 3.90 (3H, s); 5.34 (4H, s); 7.01 (1H, s); 7.43 (2H, s); 7.58 (2H, m); 7.74 (4H, m); 7.91 (2H, d); 9.02 (1H, s); 9.52 (1H, s); 11.57 (1H, br s).

EJEMPLO U

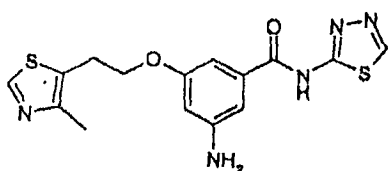
2-[3-{2-(4-Metil tiazol-5-il) etoxi}-5-dimetilamino] benzoilamino]-
[1,3,4]-tiadiazol

(Ruta 19)

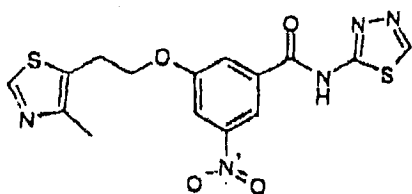


Formaldehído (37% en agua) (0.033ml, 0.44mM) se agregó a 2-[3-{2-(4-metil tiazol-5-il)etoxi}-5-amino]benzoilamino]-[1,3,4]-tiadiazol (27mg 0.074mM) y mallas moleculares 4A (0.2g) en metanol (4ml)/acetonitrilo (3ml)/ g.AcOH (2 gotas) bajo una atmósfera inerte a temperatura ambiente. Después de 150 minutos 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:

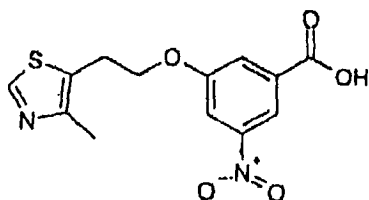


10% Paladio sobre carbono (80mg) se agregó bajo una atmósfera de argón a una solución de 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-nitro] benzoilamino]-[1,3,4]-tiadiazol (0.38g, 0.99 mM) en acetato de etilo (40ml). Se introdujo gas de hidrógeno y la mezcla de reacción se agitó vigorosamente durante 18 horas 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 trituroó 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,

2H), 7.89 (m, 1H), 8.09 (s, 1H), 8.47 (s, 1H), 8.81 (s, 1H), 9.24 (s, 1H).

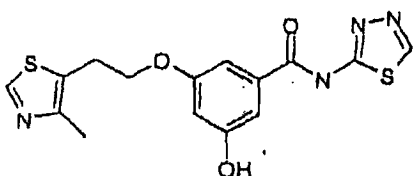


DIAD (3.16ml, 16.1 mM) se agregó a una solución agitada de 3-nitro hidroxil benzoato de metilo (2.11 g, 10.7mM), 4-(2-hidroxi etil)-5-metiltiazol (1.55ml, 12.8mM), y trifenilfosfina (4.21g, 16.1 mM) en THF (50ml) bajo una atmósfera de argón a temperatura ambiente. Después de 1 hora la mezcla de reacción 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).

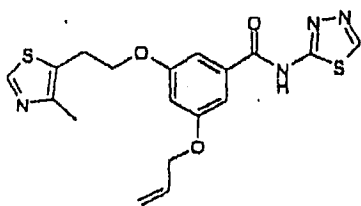
EJEMPLO V

2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-hidroxi] benzoilamino]-[1,3,4]-tiadiazol

(Ruta 20)



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) $^-$.

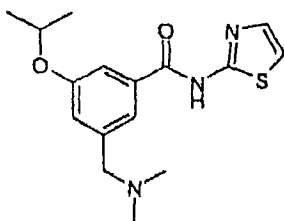


El material inicial 2-[3-{2-(4-metil tiazol-5-il) etoxi}-5-aliloxi] benzoilamino]-[1,3,4]-tiadiazol requerido se preparó de acuerdo con el método de alquilación genérico apropiado, y el ácido benzoico resultante se acopló con 1,3,4-tiadiazol de acuerdo con Ruta 1. Los datos analíticos de todos los intermedios 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,

100
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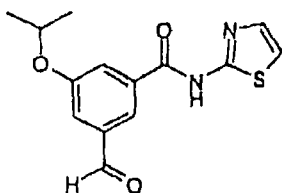
0.39mmol) en diclorometano se trató con dimetilamina (0.074ml de una solución de aprox. 5.6M en etanol, 0.41mmol, 1.1 eq) y se agitó bajo argón durante 10 minutos. A la solución se agregó tris-acetoxi borohidruro de sodio (0.11g, 0.53mmol, 1.4 eq) y la mezcla resultante se agitó durante la noche a temperatura 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

191
180

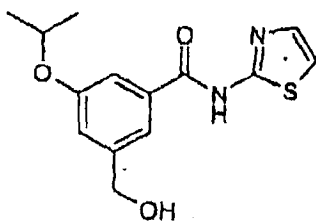
porciones) hasta que el material inicial se consumió (tlc). La suspensión se filtró, el residuo se lavó bien con acetato de etilo, y el filtrado combinado y los lavados se evaporaron *in vacuo* para proporcionar el producto como un sólido amarillo pálido, ^1H NMR δ (d_6 -DMSO): 1.31 (d, 6H), 4.82 (m, 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:

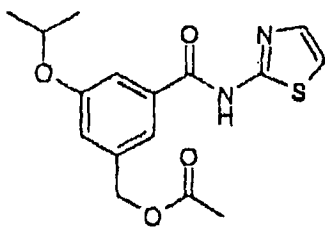
EJEMPLO Y

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).

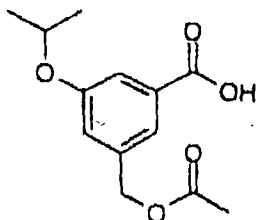


El 2-(3-isopropoxi-5-acetoximetil)benzoil aminotiazol requerido se preparó por un acoplamiento estándar entre 3-isopropoxi-5-acetoximetil benzoil cloruro y 2-aminotiazol de acuerdo con Ruta 1, para producir el compuesto

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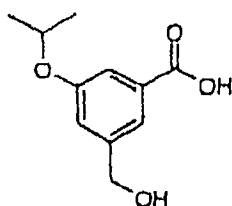
del título como un aceite amarillo pálido, δ (d_6 -DMSO): 1.3 (d, 6H), 2.1 (s, 3H), 4.75 (hept, 1H), 5.1 (s, 2H), 7.15 (s, 1H), 7.25 (d, 1H), 7.65 (d, 1H), 7.6 (m, 2H), 12.6 (bs, 1H).

El ácido 3-isopropoxi-5-acetoximetil benzoico requerido se preparó como sigue:



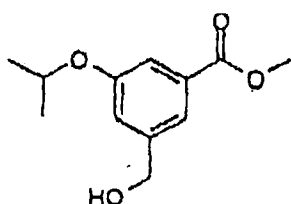
Una solución de ácido 3-isopropoxi-5-hidroximetil benzoico (0.77g, 3.7mmol) en diclorometano (20ml) se enfrió (baño helado) y se agitó bajo argón; se agregó piridina (1.18ml, 14.6mmol, 4eq) seguida gota a gota por cloruro de acetilo (0.55ml, 7.7 mmol, 2.1 eq). La mezcla se agitó durante 5 minutos, luego 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 CHl 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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XZ

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).

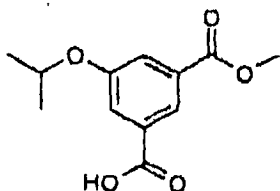
El material inicial requerido metil 3-isopropoxi-5-hidroximetil benzoato se preparó como sigue:



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/isohexano) 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).

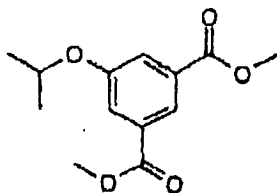
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23

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.

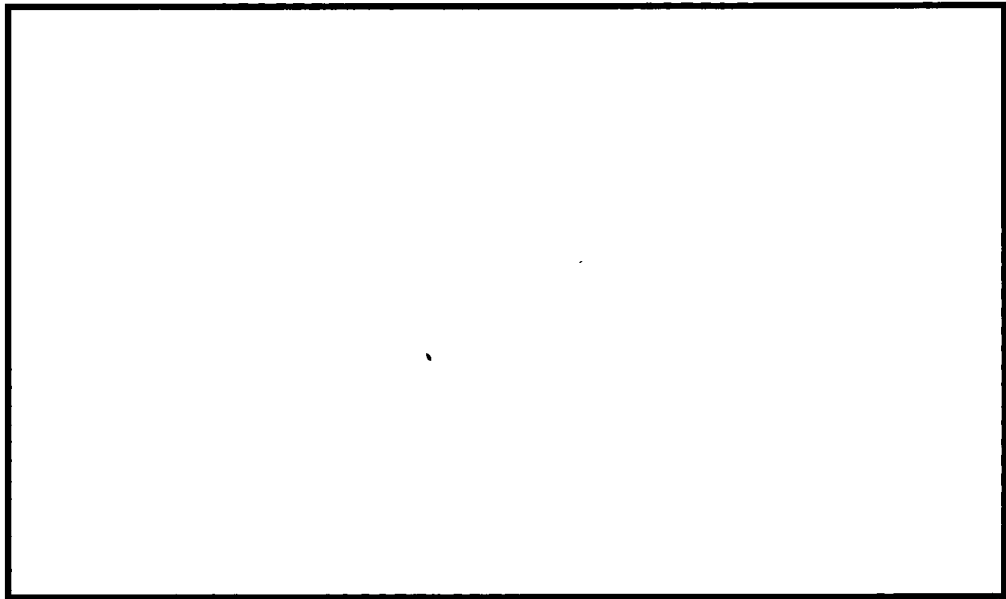
EJEMPLO Z

10

ANEXOS

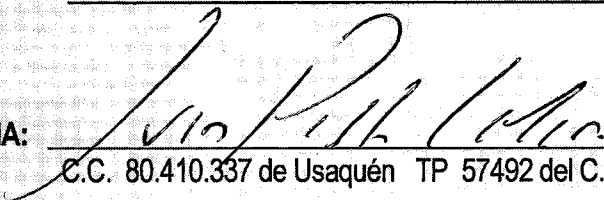
- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$501.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☒ Documento de cesión del inventor al solicitante o a su causante. **Fotocopia autenticada**
- ☐ 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.
- ☒ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Extracto para Publicación y Tarjeta de Archivo Temático
 - Tarjeta de Propietarios
 - Documentos PCT

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA: 
C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

As. 106345
4/5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 15,951
FECHA : FEBRERO 22 DE 2008



***** CONSIGNACION *

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	2279596	22/02/2008	36,825,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL :	\$ 501,000.00

4: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE ☒ PCT/GB2002/03745

MODELO DE UTILIDAD ☐

DISEÑO INDUSTRIAL ☐

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

DOMICILIO SÖDERTALJE, SUECIA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO COMPUESTOS QUE AFECTAN LA GLUCOCINASA

CLASIFICACION _____

EXPEDIENTE No. _____

FECHA DE SOLICITUD _____

ROLLO MICROFILM _____

CERTIFICADO No. _____

FECHA DE CONCESION _____

VIGENCIA DESDE _____

HASTA _____

PRORROGA _____

CAMBIO DE NOMBRE _____

TRASPASO A _____

INVENTOR (ES) SCOTT BOYD, PETER WILLIAM RODNEY CAULKETT, RODNEY BRIAN HARGREAVES, SUZANNE

OTROS SAXON BOWKER, ROGER JAMES, CRAIG JOHNSTONE, CLIFFORD DAVID JONES Y 2 MÁS.

OFICINA DE COMUNICACIONES

54

(21) No. de solicitud: 04-022003

(22) Fecha de solicitud: 10-03-2004

(51) Clasificación Internacional:

(71) Solicitante(s): ASTRAZENECA AB

(72) Inventor (es): Scott BOYD, Peter William Rodney CAULKETT, Rodney Brian HARGREAVES, Suzanne Saxon BOWKER, Roger JAMES, Craig JOHNSTONE, Clifford David JONES, Darren MCKERRECHER, Michael Howard BLOCK.

(74) Agente: JUAN PABLO CADENA SARMIENTO

(30) Prioridad

(31) No. Prioridad

(32)

Fecha

(33)

País

0102764-8

17-08-2001

SE

FIGURA CARACTERÍSTICA

6 x 6 cm

(85) Fecha inicio fase nacional: 17-03-2005

(86) Datos relativos a la presentación de la solíc. PCT

Fecha de presentación de la solicitud: 15-08-2002

No. de solicitud: PCT/GB2002/03745

(87) Publicación internacional:

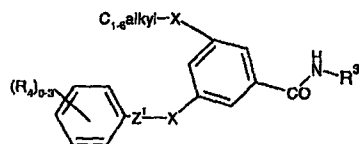
Fecha: 27-02-2003

No. Publicación: WO 2003/015774 A1

(54) Título: COMPUESTOS QUE AFECTAN LA GLUCOCINASA

(55) Reivindicación(es):

1. Un compuesto de fórmula (IIb):



Formula (IIb)

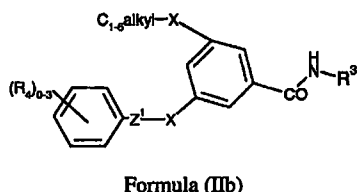
CONTINUA AL RESPALDO ...

7 6

 Industria y Comercio SUPERINTENDENCIA		SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES EXTRACTO PARA PUBLICACIÓN SOLICITUD DE PATENTE DE INVENCION PCT	
(21) No. de solicitud: 04-022003		(51) Int Cl:	
(22) Fecha de solicitud: 10-03-2004		(71) Solicitante (s): ASTRAZENECA AB	
(30) Prioridad	(31) No. Prioridad	(32) Fecha	(33) País
	0102764-8	17-08-2001	SE
		(72) Inventor(es): Scott BOYD, Peter William Rodney CAULKETT, Rodney Brian HARGREAVES, Suzanne Saxon BOWKER, Roger JAMES, Craig JOHNSTONE, Clifford David JONES, Darren MCKERRECHER, Michael Howard BLOCK.	
		(74) Agente: JUAN PABLO CADENA SARMIENTO	
(85)	(85) Fecha inicio fase nacional: 17-03-2005		(87) Publicación internacional
(86)	Datos relativos a la presentación de la solíc. PCT		Fecha: 27-02-2003
	Fecha de presentación de la solicitud: 15-08-2002		No. publicación: WO 2003/015774 A1
	No. de solicitud: PCT/GB2002/03745		
(54) Titulo: COMPUESTOS QUE AFECTAN LA GLUCOCINASA			

(55) Reivindicación(es):

1. Un compuesto de fórmula (IIb):



en donde:

cada grupo C₁₋₆ alquilo es opcionalmente sustituido con hasta 3 grupos seleccionados de R⁴, y opcionalmente contiene un doble enlace;

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;

cada Z es independientemente un enlace directo, C₂₋₆alquenileno o un grupo de la fórmula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q;

cada R⁴ se selecciona independientemente de halo, -CH_{3-a}F_a, CN, NH₂, C₁₋₆alquilo, -OC₁₋₆alquilo, -COOH, -C(O)OC₁₋₆alquilo, OH o fenil sustituido opcionalmente por C₁₋₆alquilo o -C(O)OC₁₋₆alquilo;

o R⁵-X¹-, donde X¹ es independientemente como se define en X más arriba y R⁵ se selecciona de hidrógeno, C₁₋₆alquilo, -CH_{3-a}F_a, fenilo, naftilo, heterocicilo o C₃₋₇cicloalquilo; y R⁵ se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: halo, C₁₋₆alquilo, OC₁₋₆alquilo, -CH_{3-a}F_a, CN, OH, NH₂, COOH, o -C(O)OC₁₋₆alquilo,

cada Z¹ es independientemente un enlace directo, C₂₋₆alquenileno o un grupo de la fórmula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q;

R³ es heterocicilo, en donde el átomo en la posición dos del anillo de heterocicilo relativo al grupo amida, al cual está unido R³, es un nitrógeno hibridizado sp², y R³ es opcionalmente sustituido por hasta dos grupos R⁷;

R⁶ se selecciona independientemente de hidrógeno, C₁₋₆alquilo o -C₂₋₄alquil-O-C₁₋₄alquilo;

R^{6a} se selecciona independientemente de hidrógeno, halo, C₁₋₆alquilo o -C₂₋₄alquil-O-C₁₋₄alquilo;

cada R⁷ se selecciona independientemente de:

C₁₋₆alquilo, C₂₋₆alquenilo, C₂₋₆alquinilo, (CH₂)₀₋₃arilo, (CH₂)₀₋₃heterocicilo, (CH₂)₀₋₃C₃₋₇cicloalquilo, OH, C₁₋₆alquilo, OH, halo, C₁₋₆alquil-halo, OC₁₋₆alquilo, (CH₂)₀₋₃S(O)₀₋₂R⁸, SH, SO₃, tioxo, NH₂, CN, (CH₂)₀₋₃NHSO₂R⁸, (CH₂)₀₋₃COOH, (CH₂)₀₋₃-O-(CH₂)₀₋₃R⁸, (CH₂)₀₋₃C(O)(CH₂)₀₋₃R⁸, (CH₂)₀₋₃C(O)OR⁸, (CH₂)₀₋₃C(O)NH₂, (CH₂)₀₋₃C(O)NH(CH₂)₀₋₃R⁸, (CH₂)₀₋₃NH(CH₂)₀₋₃R⁸, (CH₂)₀₋₃NHC(O)(CH₂)₀₋₃R⁸; (CH₂)₀₋₃C(O)NHSO₂-R⁸ y (CH₂)₀₋₃SO₂NHC(O)-R⁸ en donde una cadena alquilo, anillo cicloalquilo o anillo heterocicilo dentro de R⁷ se sustituye opcionalmente por uno o más sustituyentes seleccionados independientemente de: C₁₋₄alquilo, -OH, halo, CN, NH₂, N-C₁₋₄alquilamino, N,N-di-C₁₋₄alquilamino y OC₁₋₄alquilo;

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 February 2003 (27.02.2003)

PCT

(10) International Publication Number
WO 03/015774 A1

(51) International Patent Classification: A61K 31/425,
C07D 417/12, 233/48, 285/12, 213/75, 241/20, 231/40,
237/20, 239/42, 307/66, A61P 03/10

(21) International Application Number: PCT/GB02/03745

(22) International Filing Date: 15 August 2002 (15.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0102764-8 17 August 2001 (17.08.2001) SE

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, 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.

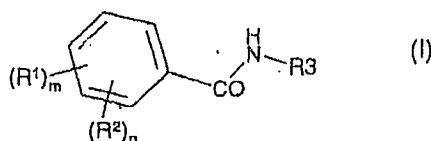
(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM,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

Published:

— with international search report

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

(54) Title: COMPOUNDS EFFECTING GLUCOKINASE



(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

10 7

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
5 *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.

10 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
15 (osetopathy).

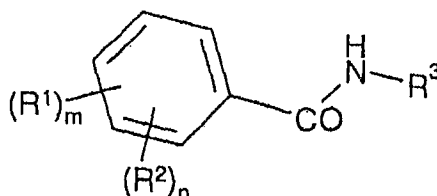
WO01/12621 describes the preparation of as isoxazolympyrimidines and related compounds as inhibitors of cJUN N-terminal kinases, and pharmaceutical compositions containing such compounds.

Cushman *et al* [Bioorg Med Chem Lett (1991) 1(4), 211-14] describe the synthesis of
20 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.
25 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
30 the biological interest of these compounds.

- or $R^5 \cdot X^1$ -, where X^1 is independently as defined in X above and R^5 is selected from hydrogen, C_{1-6} alkyl, $-CH_2F_a$, 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, $-CH_2F_a$, 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,
- 15 $(CH_2)_{0-3}S(O)_{0-2}R^8$, 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
- 20 ring within R^7 is optionally substituted by one of more substituents independently selected from: C_{1-4} alkyl, OH, halo, CN, NH_2 , $\underline{N}$ - C_{1-4} alkylamino, $\underline{N,N}$ -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 $p + q < 4$.

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;

each R^1 is independently selected from OH, $-(CH_2)_{1-4}OH$, $-CH_2F_n$, $-(CH_2)_{1-4}CH_2F_n$,

10 $-OCH_2F_n$, 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 $aryl-Z^1-$, $heterocyclyl-Z^1-$, $C_{3-7}cycloalkyl-Z^1-$,

$C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $-(CH_2)_{1-4}CH_2F_n$ or $-CH(OH)CH_2F_n$; wherein

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

each R^4 is independently selected from halo, $-CH_2F_n$, 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, $-CH_2F_a$, 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, $-CH_2F_a$, 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:

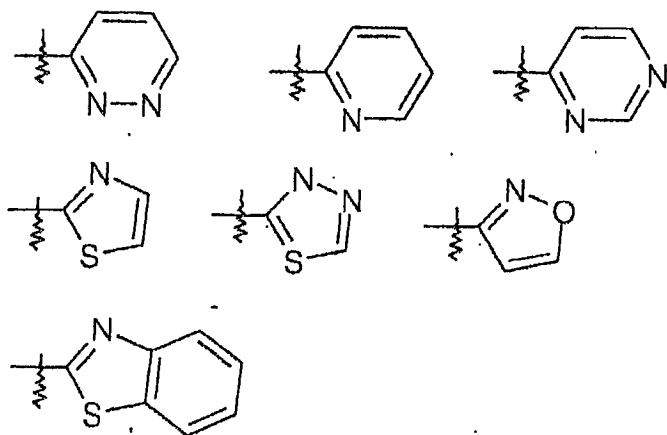
C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_{0-3}$ aryl, $(CH_2)_{0-3}$ heterocyclyl, $(CH_2)_{0-3}$ C_{3-7} cycloalkyl, OH, C_{1-6} alkyl-OH, halo, C_{1-6} alkyl-halo, OC_{1-6} alkyl, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3 , thioxo, NH_2 , CN, $(CH_2)_{0-3}NHSO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$; $(CH_2)_{0-3}C(O)NHSO_2-R^8$ 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} alkyl $OC(O)C_{1-6}$ 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;

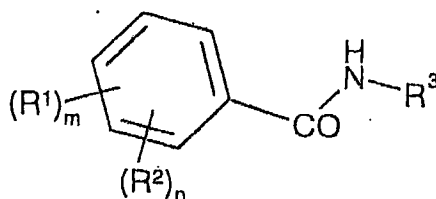
p is an integer between 0 and 3;

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-aF_a , $(CH_2)_{1-4}CH_3-aF_a$,

15 OCH_3-aF_a , 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 $Y-X-$

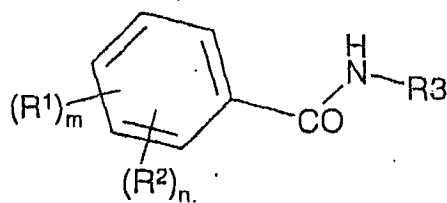
wherein each X is a linker independently selected from

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

20 $-O_2(CH_2)_{0-3}-$, $-NH SO_2-$, $-SO_2NH-$, $-N(CH_2)_{0-3}-$, $-N(CH_2)_{1-3}O(CH_2)_{0-3}-$, $-(CH_2)_{1-4}-$,

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

- 13 -



Formula (Id)

wherein

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

5 $m, n, R^1, R^2, X, Y, R^4, R^5, R^6, R^7, R^8$, 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.

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

The expression " $-CH_3-aF_a$ " 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 $-(CH_2)_{1-4}CH_3-aF_a$, 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

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,

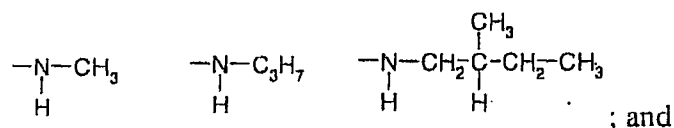
- 5 benzisoxazolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinoliny, isoquinoliny, quinoxaliny, quinazoliny, phthalaziny, cinnoliny and naphthyridiny.

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,

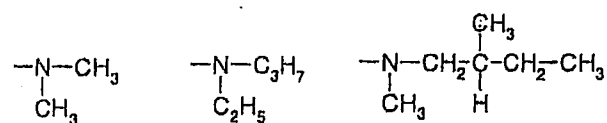
- 10 cyclopentyl or cyclohexyl.

Examples of C₁₋₆alkyl include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl and 2-ethyl-butyl; examples of C₁₋₆alkyl-OH include hydroxymethylen and hydroxyethylene; examples of C₁₋₆alkyl-halo include chloromethylene, fluoromethylene, chloroethylene and fluoroethylene; examples of C₂₋₆alkenyl include: ethenyl, 2-propenyl, 2-butenyl, or

- 15 2-methyl-2-butenyl; examples of C₂₋₆alkynyl 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)OC₁₋₆alkyl 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 (IIk) 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

-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
5 -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-,

10 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-.

15 and each Y is independently selected from:

C₁₋₆alkyl, C₂₋₆alkenyl, aryl-Z¹-, heterocyclyl-Z¹-, C₃₋₇ cycloalkyl(CH₂)₀₋₂,

-(CH₂)₁₋₄CH_{3-a}F_a;

preferably each Y is selected from:

C₁₋₆alkyl (preferably a branched chain C₂₋₆ alkyl such as isopropyl, isobutyl, etc) ,

20 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-,
piperidiny-Z¹-, piperazinyl-Z¹-, pyrrolidiny-Z¹-, tetrahydro-2H-pyranyl-Z¹-,
25 isoxazolyl-Z¹-, oxazolyl-Z¹-, pyridyl-Z¹-, thiazolyl-Z¹-, thienyl-Z¹- or
isoindolinyl-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;

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

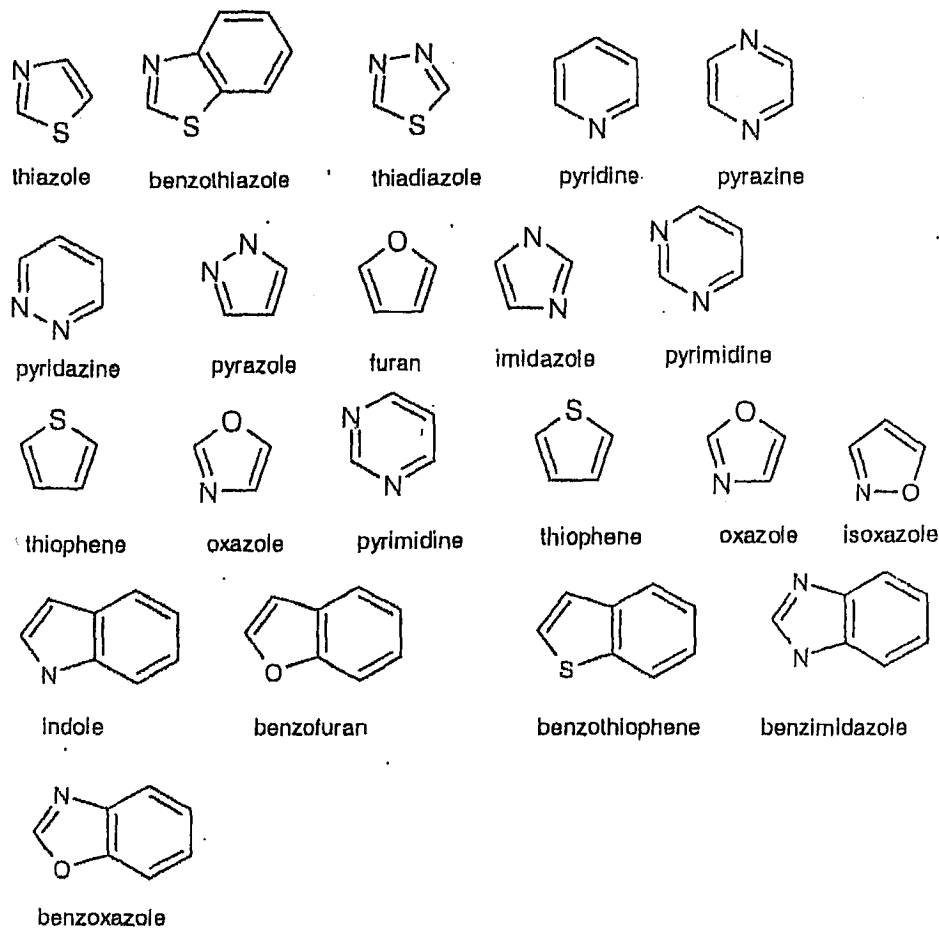
-(CH₂)_p-C(R^{6a})₂-(CH₂)_q-, wherein R^{6a} is independently selected from hydrogen
and C₁₋₂alkyl and p and q are independently 0 or 1;

Most preferably optional substituents on R^5 are independently selected from:

OH, CH_3 , t-butyl, OCH_3 , 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:

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

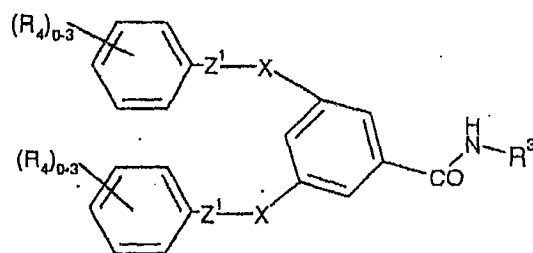
m is 0 and n is 2, the two R^2 groups are attached at the 2- and 5- or the 3- and 5- positions (ideally the 3- and 5- positions), X is $-O(CH_2)_{0-2}-$ (ideally $-O-$ or $-OCH_2-$), and R^3 is a heterocyclyl optionally substituted by R^7 ; or

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:

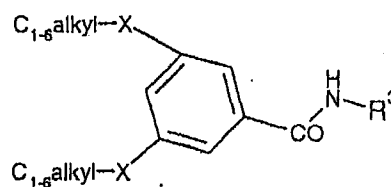
X , Z^1 , R^3 and R^4 are as defined above in a compound of Formula (I); or a salt, solvate or pro-drug thereof.

(II) a compound of Formula (IIa)

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

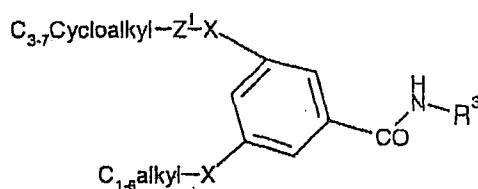
of the C_{1-6} alkyl groups contain a double bond, preferably neither of the C_{1-6} alkyl group

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;

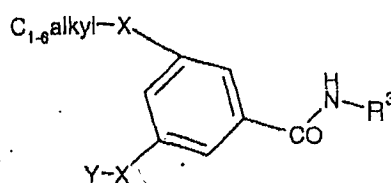
the C_{1-6} alkyl group optionally contains a double bond, preferably the C_{1-6} alkyl group does not contain a double bond; and

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.

(VII) a compound of Formula (IIIf)

(IX) a compound of Formula (IIIh)

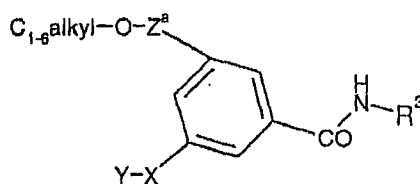


Formula (IIIh)

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;
 Z^a is selected from a direct bond or a group of the formula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q-;
 20 preferably Z^a is selected from C₁₋₂alkylene or a direct bond; preferably Z^a 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

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

15 or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include

C₁ to C₆alkoxymethyl esters for example methoxymethyl, C₁ to ₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃ to ₈cycloalkoxycarbonyloxyC₁ to ₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁-₆alkoxycarbonyloxyethyl 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

According to another aspect of the invention there is provided the use of a compound of Formula (Ib) to (Id), or (II) to (IIk), 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
5 combined treatment of obesity and diabetes by administering an effective amount of a compound of Formula (Ib) to (Id), or (II) to (IIk), 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
10 (Id), or (II) to (IIk), 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
15 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).

20 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
25 example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic 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
30 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.

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
5 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,
10 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
15 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
20 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),
25 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
30 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

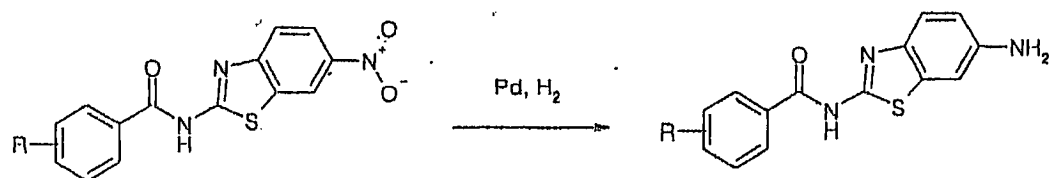
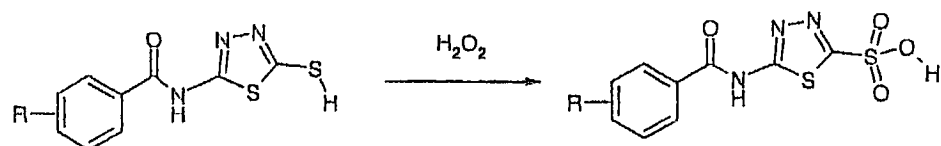
(cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);

- 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).

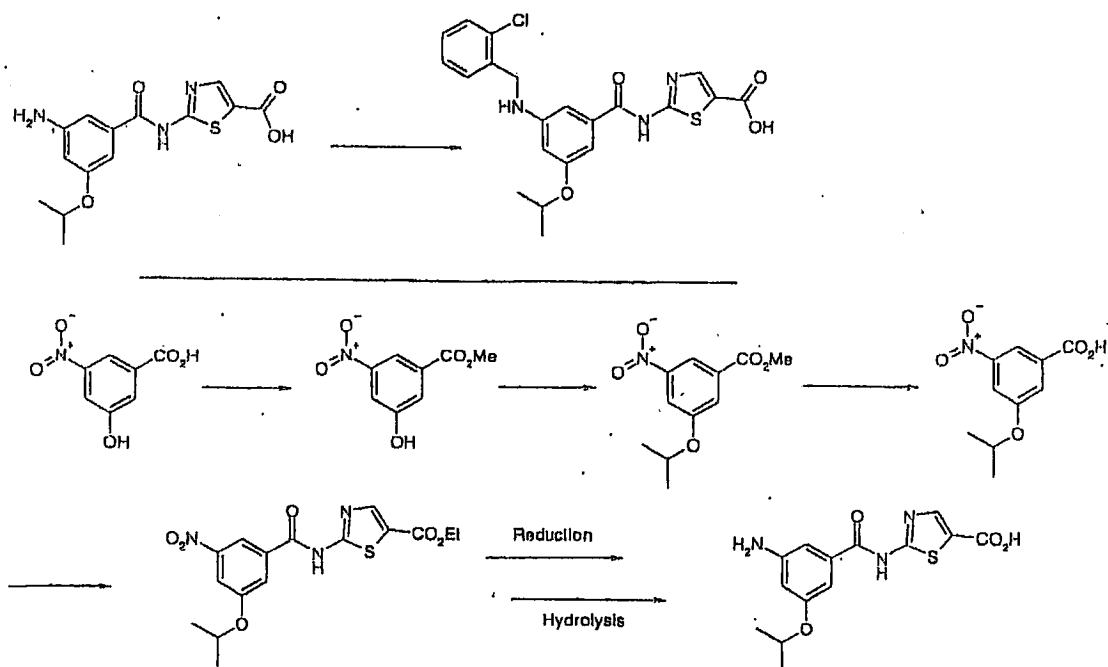
According to another aspect of the present invention there is provided individual
compounds produced as end products in the Examples set out below and salts, solvates and
15 pro-drugs thereof.

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.

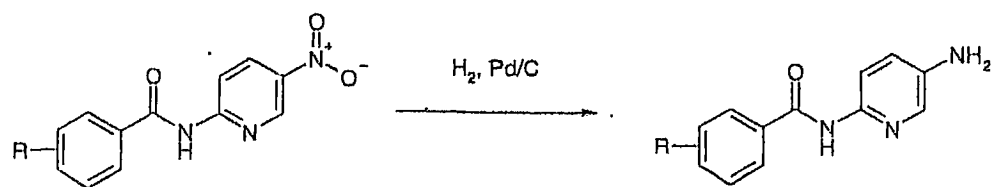
25 The condensation of an acid with a heterocyclic amine (Route 1) is used in the
preparation of compounds of the invention or in the preparation of intermediates to the final
products. One or more further reactions (such as ester hydrolysis, Routes 2a and 2b) may then
be performed on these intermediates. 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

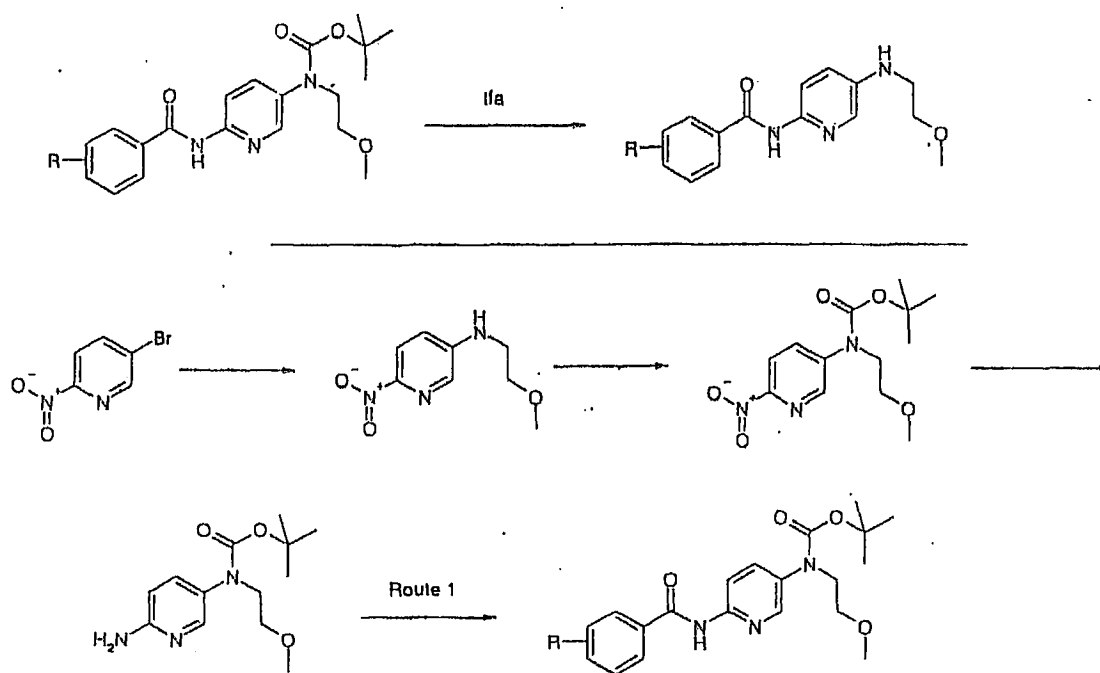
Route 45 Route 5Route 6

10

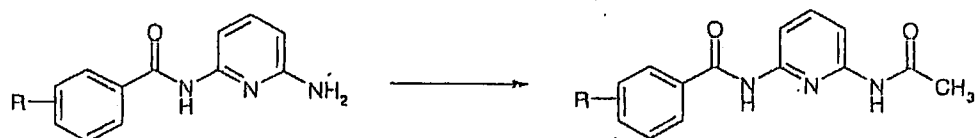
Route 7

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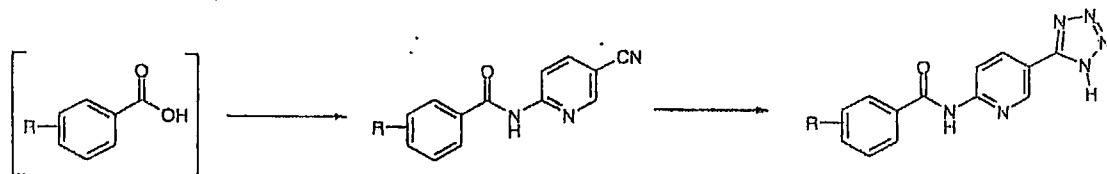


Route 11

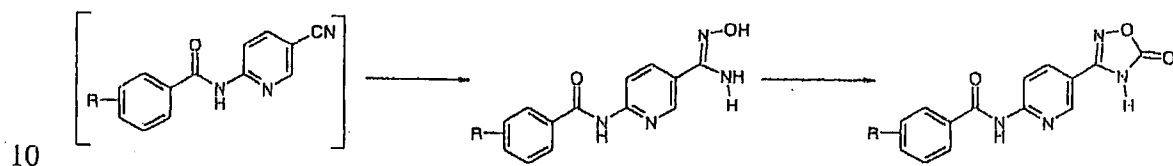
Route 15



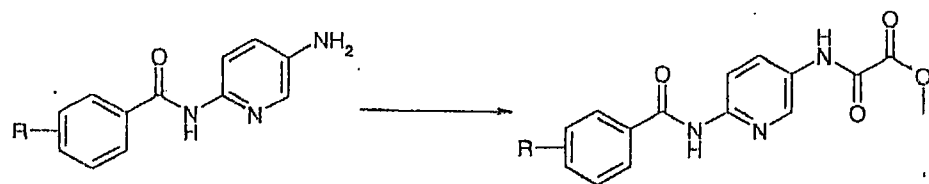
5 Route 16



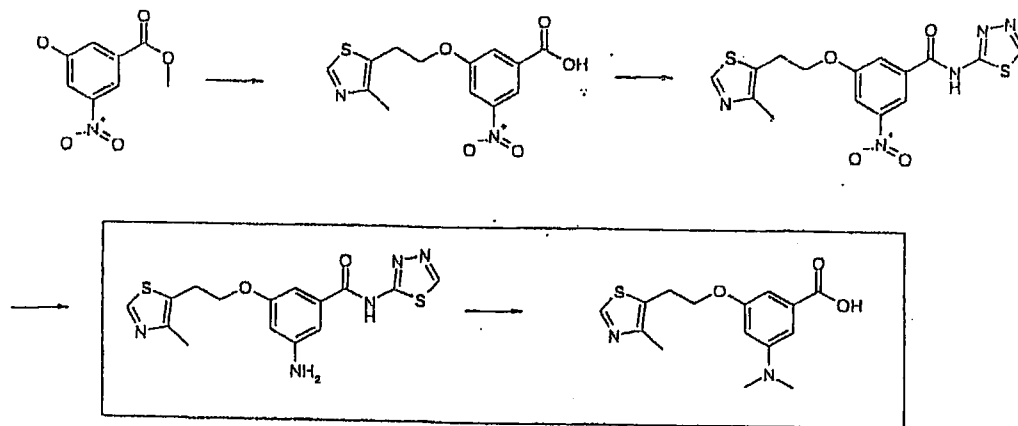
Route 17



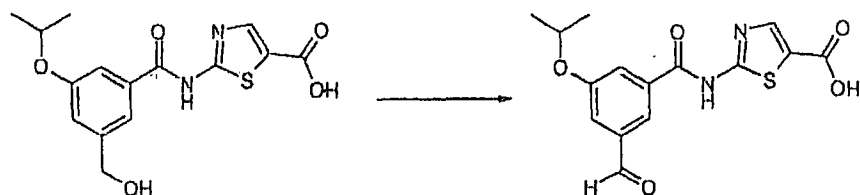
Route 18



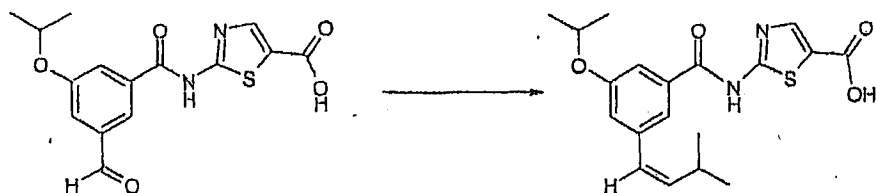
Route 19:



Route 24:

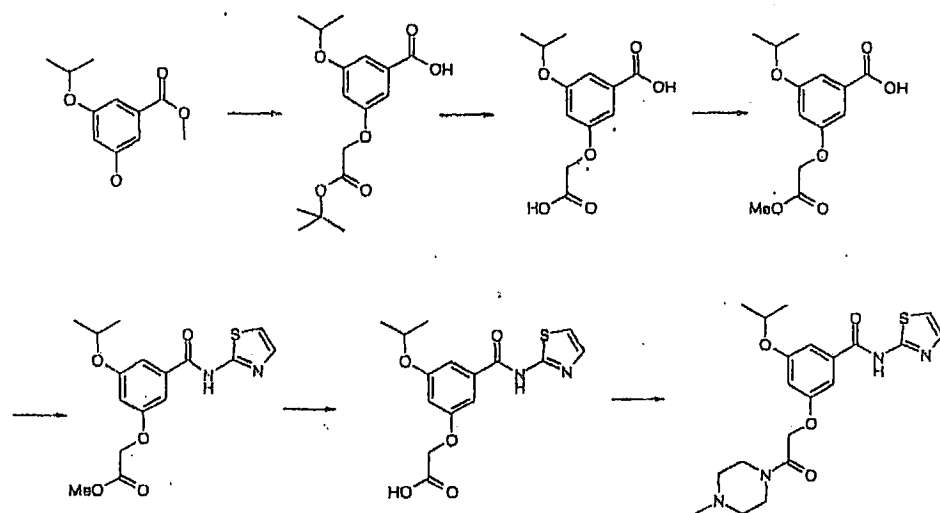


5 Route 25:



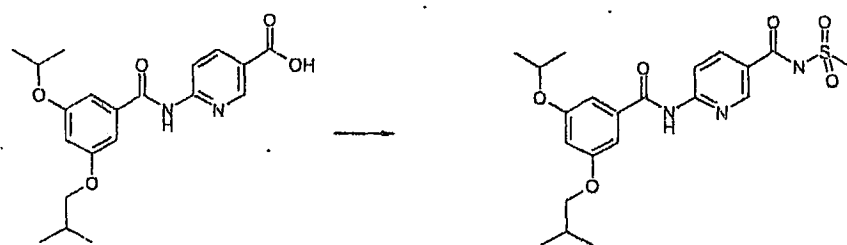
Route 26:

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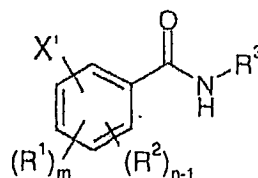


Route 27:

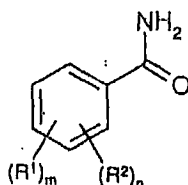
15



- (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

10 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
 25 such as palladium on carbon or cuprous iodide;

31 30

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.

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

15 Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

- 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. 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
- 25 (2-6C)alkenyl groups (e.g. allyl and vinyl ethyl).
- 30

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

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;

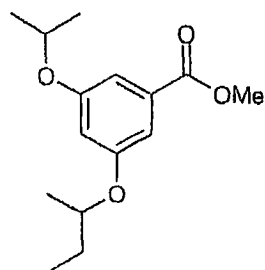
(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Silica gel 60, 0.040 - 0.063
20 nm, 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;

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 (MgSO_4), 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 (d_6 -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).
- 15 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 (MgSO_4), 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 (d_6 -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)+.

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).

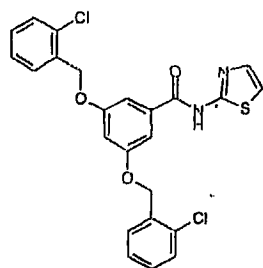
- 5 The above generic methods are for illustration only; it will be appreciated that alternative conditions that may optionally be used include: use of alternative solvents (such as acetone or tetrahydrofuran), alternative stoichiometries of reagents, alternative reaction temperatures and alternative 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, 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, m); 7.50 (2H, m); 7.55 (1H, d); 7.61 (2H, m); 12.60 (1H, br s).
- 15
20

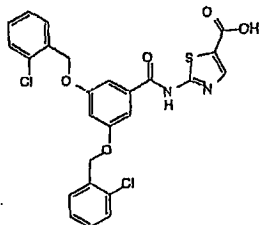
- Alternative conditions that may optionally be used include: use of an alternative solvent, such as tetrahydrofuran; use of pyridine as solvent, with or without the addition of DMAP or DIPEA; dissolving the acid chloride component in the solvent of choice, and adding the amine component to it.
- 25

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

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



10

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).

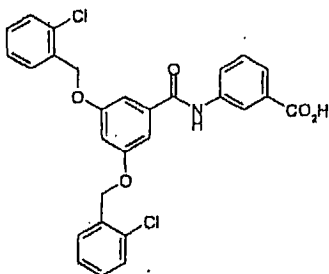
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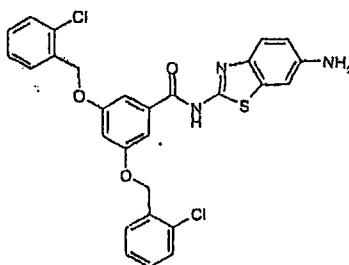
The requisite starting material was prepared by a route analogous to that given in Example A.

20

EXAMPLE C

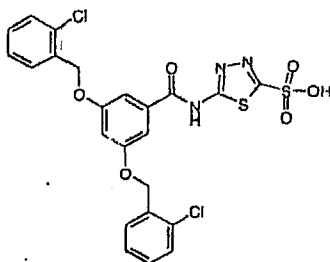
Route 2b: [3,5-di-(2-chlorobenzoyloxy)benzoyl] aminobenzene-3-carboxylic acid



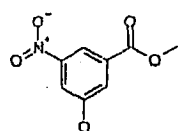
EXAMPLE ERoute 4: 2-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-6-aminobenzothiazole

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).

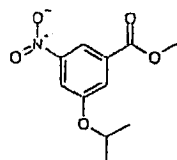
EXAMPLE F20 Route 5: 5-[3,5-Di-(2-chlorobenzoyloxy)benzoyl]amino]-[1,3,4]thiadiazole-2-sulfonic acid

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



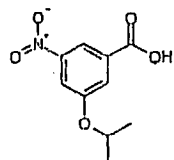
Compound (d)

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 15 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).



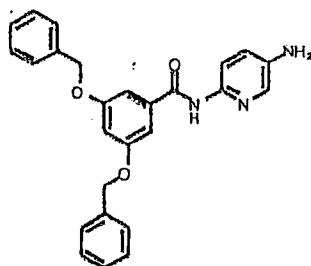
20 Compound (f)

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- 25 vacuum over silica gel. Compound (f) was obtained as an off-white solid (1.04g, 94%); ¹H

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



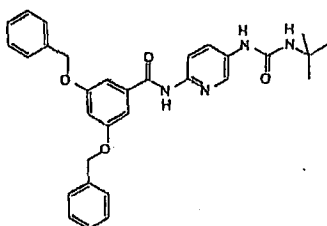
To a stirred solution of 2-[(3,5-dibenzyloxybenzoyl)amino]-5-nitropyridine (910 mg) in DMF (6 ml) was added Zinc dust (1300 mg) and a solution of ferric chloride hexahydrate (1700 mg) in water (6 ml). The resulting mixture was stirred at 120°C for three hours. Allowed to cool to ambient temperature. 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)⁺.

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

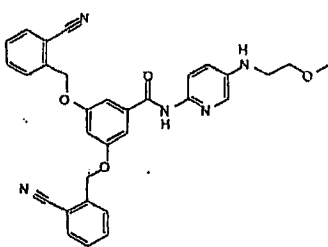
5 Route 10: 3,5-dibenzyloxy-N-[(5-[(*tert*-butylamino)carbonyl]amino)pyridin-2-yl]benzamide



A solution of *tert*-butyl isocyanate (51 mg) in THF (5 ml) was treated with 2-[(3,5-dibenzyloxybenzoyl)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

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



20

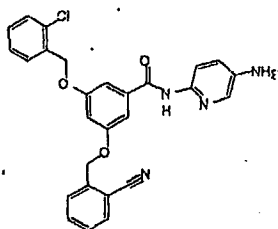
To a stirred solution of *tert*-butyl 6-[(3,5-di(2-cyanobenzoyloxy)benzoyl)amino]pyridin-3-yl(2-methoxyethyl)carbamate (237 mg) in dichloromethane (10 ml) was added trifluoroacetic acid (3 ml). The solution was stirred at ambient temperature for three hours. Volatile material was removed by evaporation. 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

- 63 -

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

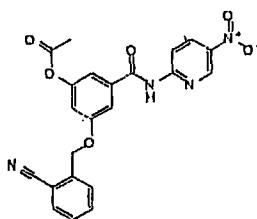


The title compound was prepared from *N*-(5-nitropyridin-2-yl)-3-[(2-chlorobenzyl)oxy]-5-[(2-cyanobenzyl)oxy]benzamide using a method similar to that described in Route 7.

10

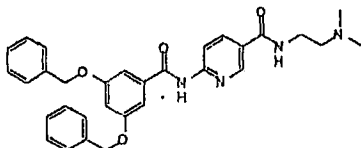
The requisite starting materials were prepared as follows:

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

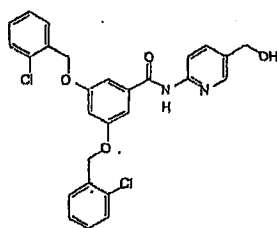


- 15 To a stirred solution of 3-acetoxy,5-(2-cyanobenzyl)oxy)benzoic acid (8760 mg) in THF (100 ml) was added Oxalyl chloride (3.6 ml) and DMF (0.5 ml). The mixture was stirred at ambient temperature for 3 hours. Volatile material was removed by evaporation. The residue was dissolved in a mixture of 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

EXAMPLE NRoute 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).

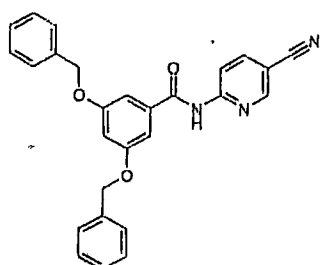
15 EXAMPLE ORoute 14: 2-[3,5-Di-(2-chlorobenzyloxy) benzoylamino]-5-hydroxymethyl pyridine

- 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

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

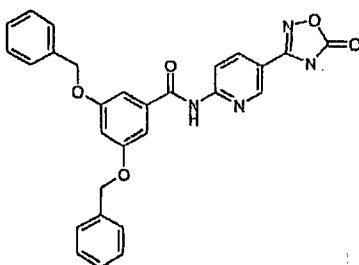


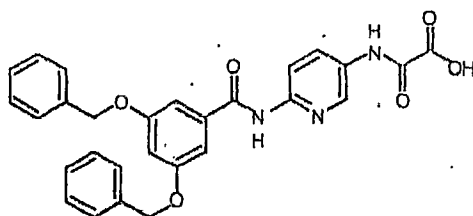
The title compound was prepared as described in Example A (route 1), starting from 2-amino-5-cyanopyridine and 3,5-bis(benzyloxy) benzoyl chloride, ¹H NMR δ (d₆-DMSO): 5.19 (4H, s); 6.89 (1H, m); 7.26-7.46 (12H, m); 8.27 (1H, dd); 8.33 (1H, d); 8.84 (1H, s); 11.23 (1H, br s); ^{m/z} (LCMS; ESI+) 436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



EXAMPLE SRoute 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^+).

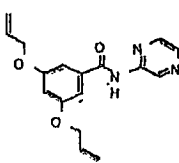
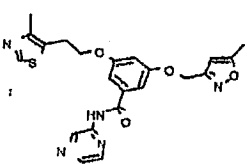
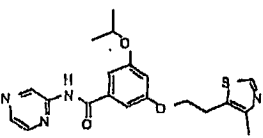
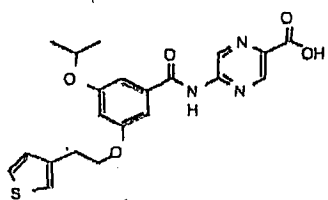
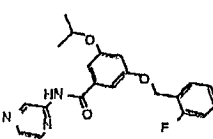
The requisite starting material was prepared according to Example H (route 7).

EXAMPLE T:

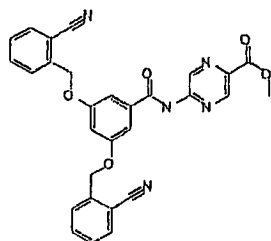
20 By analogous methods to those described above the following compounds, Example numbers
 T_1 to T_{20} , were also made.

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

Example	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).

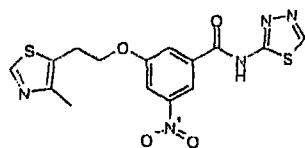
Example	Structure	Route			NMR
16		1b	312		
17		1b	452		
18		1b	400		
19		2a, 1c	428	426	δ_H (500MHz, DMSO- d_6) 1.28 (6H, d), 3.07 (2H, t), 4.26 (2H, t), 4.70 (1H, m), 6.71 (1H, m), 7.12 (1H, m), 7.24 (2H, m), 7.30 (1H, m), 7.46 (1H, m), 8.98 (1H, d), 9.48 (1H, d), 11.33 (1H, s), 13.24 (1H, br s).
20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

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

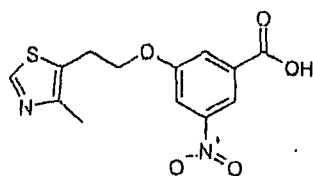


1H NMR δ (d_6 -DMSO): 3.90 (3H, s); 5.34 (4H, s); 7.01 (1H, s); 7.43 (2H, s); 7.58 (2H, m);
5 7.74 (4H, m); 7.91 (2H, d); 9.02 (1H, s); 9.52 (1H, s); 11.57 (1H, br s).

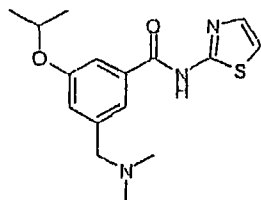
- 75 -



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).

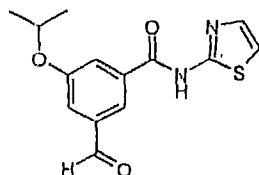
EXAMPLE W2-(3-isopropoxy-5-dimethylaminomethyl)benzoyl aminothiazole(Route 21)

- 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 (d₆-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:

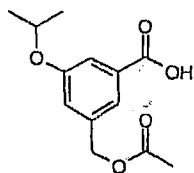
EXAMPLE X2-(3-isopropoxy-5-formyl)benzoyl aminothiazole(Route 22):

25



48 42

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

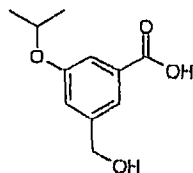


A solution of 3-isopropoxy-5-hydroxymethyl benzoic acid (0.77g, 3.7mmol) in

- 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).

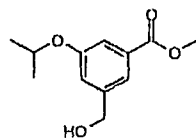
15

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:



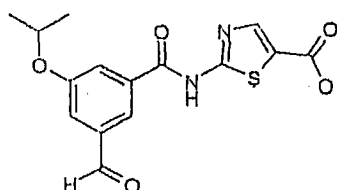
49 ~~24~~

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)



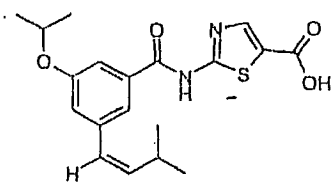
A solution of 2-(3-isopropoxy-5-hydroxymethyl)benzoyl aminothiazole-5-carboxylic acid (0.42g, 1.25mmol) in tetrahydrofuran (50ml) was treated with Dess-Martin periodinane (DMP, 0.58g, 1.37mmol, 1.1 eq) and stirred at ambient temperature for 90 mins. The solvent was removed *in vacuo*, and the residue 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 II₈₁.

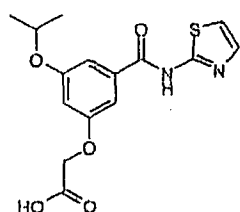
EXAMPLE AA

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

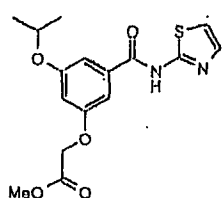
(Route 25)



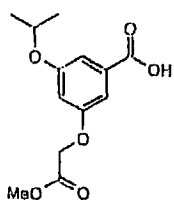
A solution of iso-butyl triphenyl phosphonium bromide (0.45g, 1.13mmol, 3.1 eq) in tetrahydrofuran (20ml) was treated with potassium t-butoxide (1.1ml of 1M in



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), 5 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 ($M-H$) $^-$



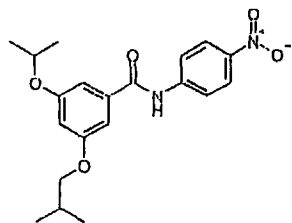
The requisite 2-(3-isopropoxy-5-methoxycarbonylmethylene oxy) benzoyl aminothiazole 10 starting material was prepared from 3-isopropoxy-5-(methoxycarbonyl)methoxybenzoic acid and 2-aminothiazole (48% isolated yield) by a standard acid chloride coupling (Route 1); ^1H NMR δ (d_6 -DMSO): 1.27 (d, 6H), 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 ($M-H$) $^-$



15 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), 20 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 ($M-H$) $^-$

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%).

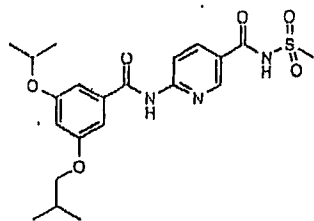
^1H NMR δ (d_6 -DMSO): 0.97 (d, 6H), 1.26 (d, 6H), 2.00 (m, 1H), 3.78 (d, 2H), 4.69 (m, 1H), 5.12 (s, 2H), 6.58 (t, 1H), 6.99 (dd, 1H), 7.1 (ap d, 2H), 7.73-7.78 (m, 2H), 10.24 (bs, 1H); m/z 344.41 ($\text{M}+\text{H}$) $^+$



- 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

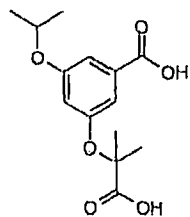
2-[(3-isobutyloxy-5-isopropoxy) benzoyl] amino -5-(N-methylsulfonyl)-carboxamido pyridine
(Route 27)



- 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),

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, 15 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)⁻.

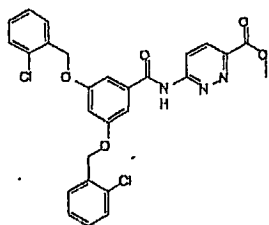
EXAMPLE FF:

By analogous methods to those described above the following pyridazine compounds,

Example numbers FF₁ to FF₅, were also made.

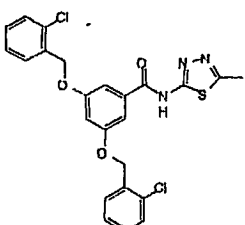
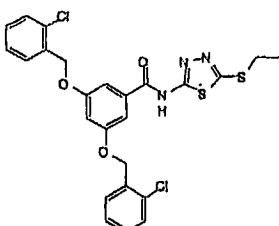
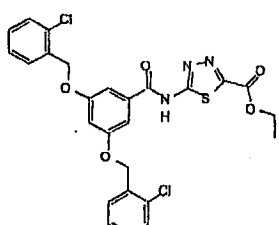
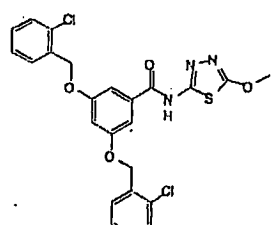
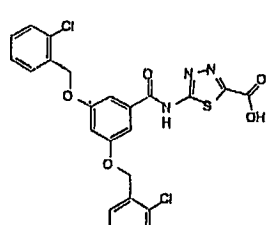
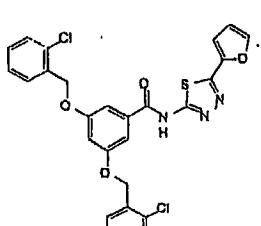
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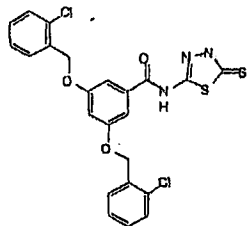
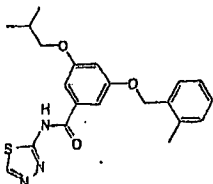
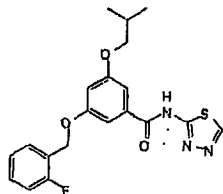
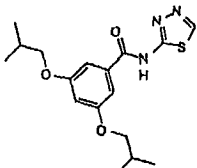
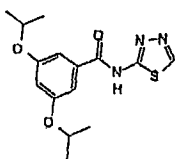
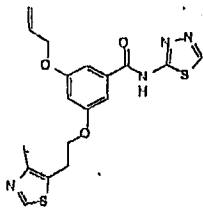
Example	Structure	Route	(M+H) ⁺	(M+H) ⁻	NMR
1		1			¹ H NMR d (d ₆ -DMSO): 3.95 (3H, s); 5.25 (4H, s); 6.95 (1H, s); 7.4 (6H, m); 7.5 (2H, m); 7.65 (2H, m); 8.25 (1H, d); 8.6 (1H, d); 11.85 (1H, br s).

**EXAMPLE GG:**

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

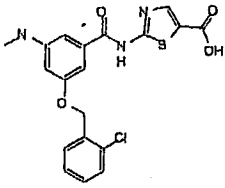
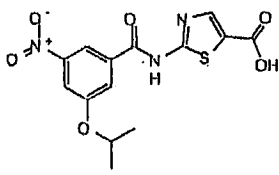
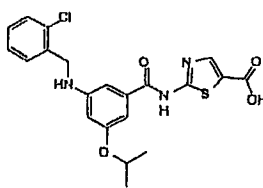
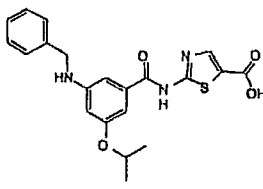
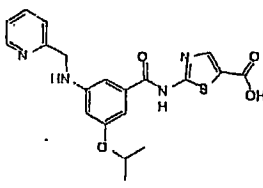
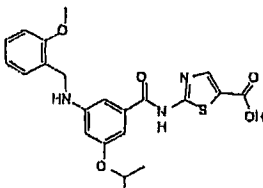
Example	Structure	Route	(M+H) ⁺	(M+H) ⁻	NMR
1		2 *			¹ H NMR d (d6-DMSO): 5.22 (4H, s); 6.54 (1H, d); 6.93 (1H, d); 7.27 (1H, d); 7.32-7.44 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 11.85 (1H, s); 12.86 (1H, br s).
2					¹ H NMR d (d6-DMSO): 3.75 (3H, s); 5.21 (4H, s); 6.55 (1H, d); 6.86 (1H, m); 7.31 (1H, 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		
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	(M+H)+	(M-H)-	NMR
2		1			¹ H 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			¹ H 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			¹ H 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			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).

Example	Structure	Route	(M+ H)+	(M+ H)+	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).

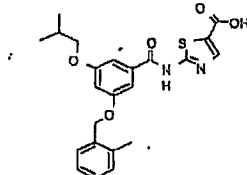
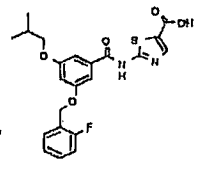
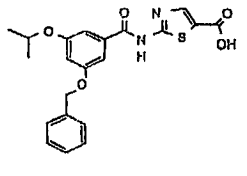
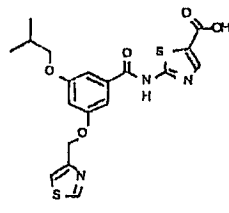
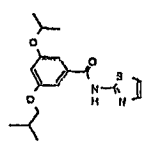
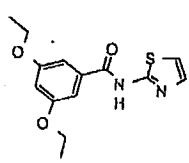
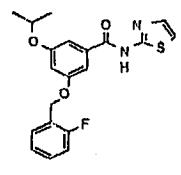
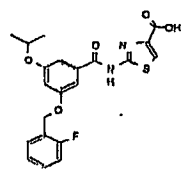
Example	Structure	Route	(M+ H)+	(M- H)-	NMR
25		1b	336		
26		1b	405		
27		2a, 1c (b)	388	386	δ_H (500MHz, DMSO- d_6) 1.27 (6H, d), 4.73 (1H, m), 5.21 (2H, s), 6.82 (1H, s), 7.20-7.31 (3H, br m), 7.36- 7.47 (2H, brm), 7.58 (1H, t), 9.23 (1H, s), 12.97 (1H, br s).
28		2a, 1c (b)	389		δ_H (500MHz, DMSO- 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).

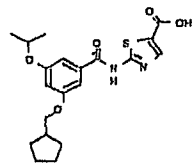
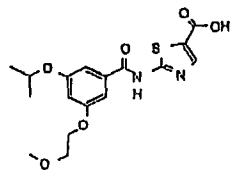
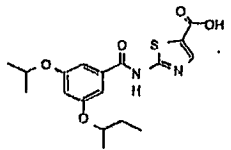
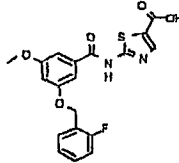
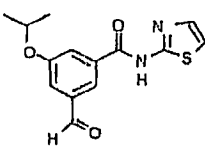
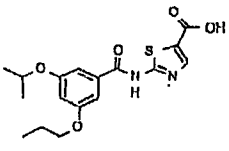
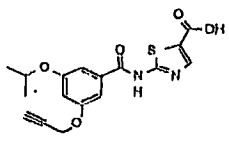
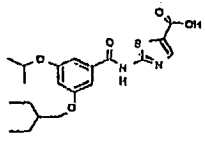
Example	Structure	Route	(M+ H)+	(M+ H)+	NMR
4		1		531	¹ H NMR d (d6-DMSO): 4.77 (2H, s); 5.25 (4H, s); 6.94 (1H, m); 7.31 (1H, s); 7.36-7.48 (6H, m); 7.53 (2H, m); 7.63 (2H, m); 12.83 (1H, br s) (+ 0.4 eq. iPr2NEt).
5		3	528, 530		¹ H NMR d (d6-DMSO): 2.63 (3H, m); 4.16 (2H, m); 5.24 (4H, s); 6.99 (1H, 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 (- CO2)	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 (- 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).

Example	Structure	Route	(M+H)+	(M-H)-	NMR
16		6			¹ H 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			¹ H 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)	¹ H 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			¹ H 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)	¹ H 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)	¹ H 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).

Example	Structure	Route	(M+H)+	(M-H)-	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).

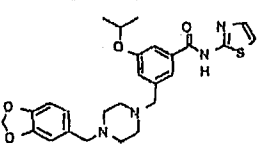
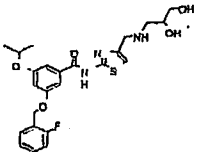
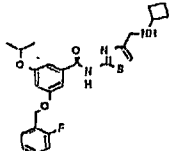
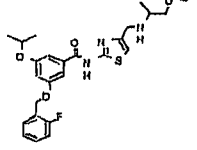
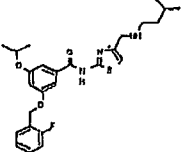
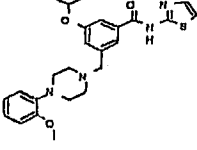
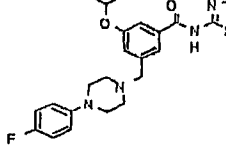
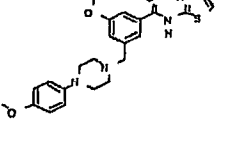
Example	Structure	Route	(M+ H)+	(M- H)-	NMR
39		2a (1)			¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.17 (s, 4H), 6.93 (s, 1H), 7.29-7.45 (m, 7H), 7.53 (s, 1H), 8.13 (m, 1H).
40		1			¹ H NMR δ (d ₆ -DMSO): 2.64 (s, 3H), 5.14 (s, 4H), 6.90 (s, 1H), 7.26 (d, 1H), 7.31-7.47 (m, 7H), 7.49 (m, 1H), 7.55 (d, 1H), 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).

Example	Structure	Route	(M+ H)+	(M- H)-	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).

Example	Structure	Route	(M+ H) ⁺	(M- H) ⁻	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).

Example	Structure	Route	(M+H) ⁺	(M-H) ⁻	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	(M+H) ⁺	(M+H) ⁺	NMR
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	Route	(M+H) ⁺	(M+H) ⁺	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	