Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

Division de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No** 06-316774

54 **TITULO** PIRIDINAS PIRAZINAS Y PIRIMIDINAS FUSIONADAS CON HETEROARILO COMO LIGANDOS RECEPTORES CRF1

51 **CLASIFICACIÓN INTERNACIONAL** C07D471/00 471/04, 487/04, 519/00 A61K31/4985 31/437 31/4375 A61P25/24 9/00

71 **SOLICITANTE s** NEUROGEN CORPORATION y AVENTIS PHARMACEUTICALS INC

DOMICILIOs Brandf d Connectic t y Bridgewater New Jer ey, Estados Unid d América spectivament

74 **APODERADO** EMILIO FERRERO

C C 438 019 d Usaquén

22 **BOGOTA, D C ,**

(FORMA P 0)

9097 Imprenta nacional Colombia- 2004

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINDUSTRIA Y COMERCIO
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Fech (AMD) 2006-03 30 17 25 59
Tramite 011 PCT-PATENT 378 FASE NACI 411 PRESENTAC
Dependenci 8920 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL 05 04 2006

1 SOLICITUD DE

☒ Patente de Invención ☐ Patente de Modelo de Utilidad
☒ Capítulo I ☐ Capítulo II

2 SOLICITANTE (71)

Nombre NEUROGEN CORPORATION y AVENTIS PHARMACEUTICALS INC

Sociedades constituidas y existentes bajo las leyes de Estados Unidos de América

Dirección 35 Northeast Industrial Road
Brandford
Connecticut 06405
Estados Un dos de América y

300 Summerset Corporate
Boulevard
Bridgewater
New Jersey 08807 2854
Estados Unidos de América

Domicilio Brandford
Connecticut 06405
Estados Unidos de América y

Bridgewater
New Jersey 08807 2854
Estados Un dos de América

IDENTIFICACIÓN
C C ☐ NIT ☐
C E ☐ Otro ☐
Cual ____
Numero ____

3 REPRESENTANTE O APODERADO

Nombre EMILIO FERRERO
Dirección Carrera 4 No 72-35
Teléfono 347 36 11
Fax 211 86 50
E-mail clientes@camyo.com
Domicilio Bogotá Colombia

IDENTIFICACIÓN
C C ☒ NIT ☐
C E ☐ Otro ☐
Cual ____
Número 438 019 T P 31 929

4 INVENTOR (ES) (72)

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Estados Unidos de América

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Estados Unidos de América

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Estados Unidos de América

11 **Greg SHUTSKE**
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New Jersey 08867
Estados U idos de América

(5) **PCT (86)**
Solicitud Internacional No PCT/US2004/028899 Fecha 3 de septiembre de 2004
Publicación Internacional No WO 2005/023806 A2 Fecha 17 de marzo de 2005

(6) **Título (54)**
PIRIDINAS, PIRAZINAS Y PIRIMIDINAS FUSIONADAS CON HETEROARILO C M LIGANDOS RECEPTORES CRF1

(7) **Clasificación Internacional (51)** C07D 471/00, 471/04, 487/04, 519/00, A61K31/4995, 31/437, 31/4375, A61P25/24 9/00

(8) **Prioridad** SI☒ NO☐

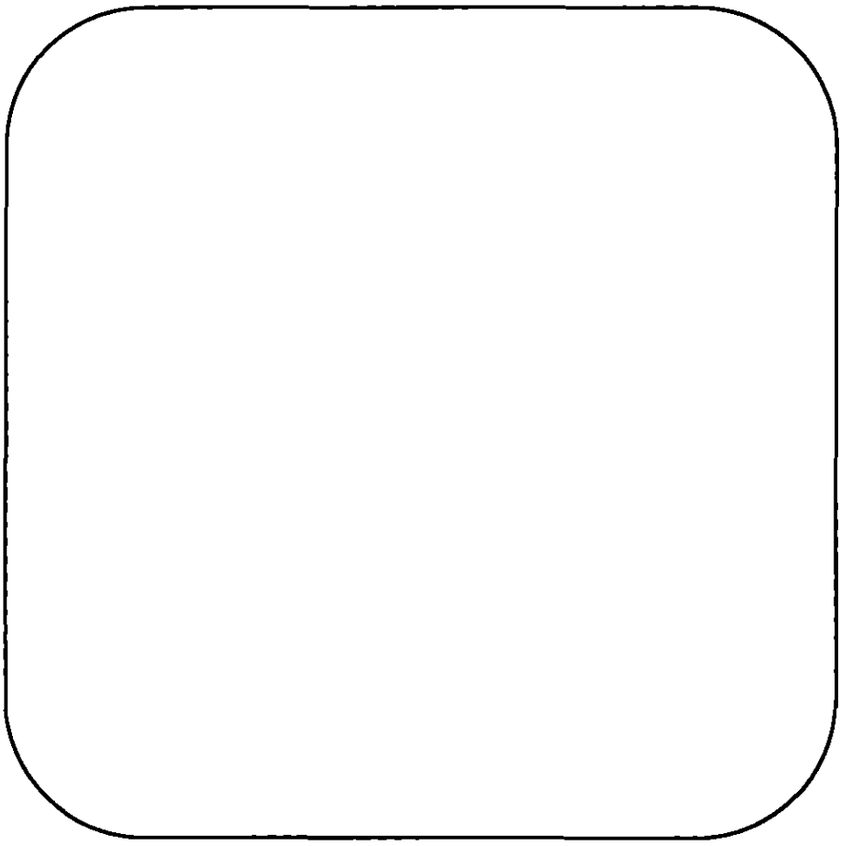
(33) País de Origen	(32) Fecha	(31) Numero de Solicitud
US	5 de septiembre de 2003	60/500.414

(9) **Comprobante de pago No** 06 22.305 **Fecha** 21 de marzo de 2006

(10) **Anexos**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 463 000 oo
- ☐ Comprobante de pago por reivindicación de prioridad
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen descripción reivindicaciones dibujos)
- ☒ Traducción de la solicitud internacional al castellano (Resumen descripción reivindicaciones dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ Traducción del examen preliminar efectuado por la IPEA
- ☐ De ser el caso copia del contrato de acceso
- ☐ De ser el caso documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso certificado de depósito del material biológico
- ☐ 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 VER HOJA DE DOCUMENTOS ANEXOS

(11) **FIGURA CARACTERÍSTICA**



(12) Solicito la concesión de la patente

NOMBRE EMILIO FERRERO

FIRMA _____

C C 438 019 de Usaquén T P 31 929

JDF

C166

CAVELIER
ABOGADOS
EDIFICIO SISKI
ARRERA # Nº 72-35
BOGOTA, COLOMBIA

For patents, utility models, industrial designs trademarks, commercial names, trade emblems slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales enseñas lemas comerciales.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

I (we) the ndersigned/Y (nosotros) abajo firmad ( )

NEUROGEN CORPORATION

of/domiciliad (s) en 35 Northeast Industrial Road Branford Connecticut United States of America

po l presente ombramos EMILIO FERRERO tpa. 31929 GONZALO PERDOMO tpa 831, LUZ CLEMENCIA DE PAEZ, tpa 23555 y GERMAN CAVELIER, tpa 832, d mi iliados la Carrera 4 Nº 72-35 Bogotá Colombia en bedecimiento lo dispuesto l parágrafo 1 d l Artícul 543 d l Código d Comerci l primero com principal y los d má com suplentes ord n, como mis (estros) represe tantes en todos los asu tos d propiedad industrial con facultad para recibi otificaci nes y ombra poderados judiciales extrajudici les. El prime representa te suplente reemplazará al pri pal en caso d se i impedimento temporal defi itivo d aq él. La misma regl se plicará cu nd l gu d represe tante suple te hay d reemplazar al primero o l tercero l segund E t les casos l represe t te principal, l primero segu d suple te su caso mbos, declararán su intenció d no jercer la representación medi te declaració te ticad por N tario Público en C lombia po Notari otro Funcionari Público Cóns l d Colombia, l extranjero y si se tratare de impedimento co l certificad respecti Si alguno d los nombrados falt re d fi iti m te l gui te tomará su l ga Cuand cesare la sencia impedimento d l repres t te principal d su prim ro segund pl tes su caso podrá jerce la representa ión, rd n, no ros segú l caso sumiénd l po l sol hech d ejerceri cesand ese m m t l jercicio d l represe t ció po l prim ro segu d tercer ple t su caso

Además co fi ro (conferimos) pod los bogados rriba nombrados para btener l proteccion d mi (estr) propiedad i d trial y co tr la competenci desle l, cuyo fecto torizo (amos) los dichos pod rados para qu m (os) represe te ante cu lesquiera tidades personas, ejerza no jurisdicció especialm te te las d l ord dmi istrativo contencioso-admi istrativo y judici l así como los ribunales d rbi ram t tod lo concernie te los sigui tes as tos) Obtenció d patentes d i vención, odelos d tilid d y diseños i d tri les l registro d marca d fábrica colectivas d fensivas d servici lemas comerciales nombres comerciales nseñas variedades vegetales y d nomi ci nes d origen, su renovación traspas cambio d ombre d micili cancelación vol taria y l registro d licencias d uso d esos derechos b) Las accione d competen la deslea, protección d l consumidor oposiciones bservaci es ca celación dministrativa y judicial lidad medid ca telares co cesión d l cencias la tela la protecció d secretos d tri les y ge er l los juicios ci iles pe ales dmi istrativos co ten ioso-admi istrati os relacion dos co tos dere hos, accione y procesos q pro novamos se nos prom evan Y para q en todos los asuntos arriba ncetermin dos puedan su titul este ma d t sustituir, conciliar, dmiti los hechos d l proceso des tir se anecta recibir renunciar y ratifica los ctos d ge tes l d compliance with the terms f paragraph 1st. f rticl 543 f the C mmerci l Code, d hereby ppoi t EMILIO FERRERO tpa 31929 GONZALO PERDOMO, tpa 831 LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled t Carrera 4 Nº 72-35 Bogotá, Colombia, th first as pri cipal d th others as ltern tes i th ord f hei ppoi tment as our representatives fo all industrial property m tters with faculty to receive notifications and to ppoi ttorneys in nd out f Court The first lternate hall replace th principal in case f his bsence or f temporal or defini ive mpedime Th sam rul will pply when th second altern te represe tative is to replace th first one or whe th thurd is to replace the first or second alternates i th i turn, or both f th m second I h cases th pri cipal represe t tive the first second ltern tes i thei turr or both of them hall tate their inte ti not t act as represe t tives through declaration give before Notary Public i Colombia or before Notary or other Publi Offici l C l mbian Consul abroad, and I case f impedime t the ppropri te certificate hall suffice If y f th ppo tees were to b d fi itely bsent th foll wi g altern te hall t k his place Whe he bsence or impedim t f th principal represe t ti or f th first second lternate i thei tu ceases th representation can be take gai in thei seq ence by th pri cipal th first or second lternate dependi g on case d th m re fact or its xercise will ffice Th xercise f th represe tio by th first second or third ltern tes i thei rn h ll end t su h tim

I dditi we gra t Power f Attorney i favor f th bove-named torneys-at-law so that they may obtain the protecti f my (ou) industrial property d gainst the fai competition, for which purpose I (we) thorize th said t rneys to represent m ( ) before y thorities or persons with or without jurisdicti pecially those admi istrative administrative co te ti and judicial, as well as before Arbitrati Court i all matters concerning th foll wing:) Obtai m t f patents, tility mod ls nd industri l des gns th registratio f trad marks collective d fensive and service marks logans commercial names, trad emblems vegetal vari ties d d mi tion f origin, its renew l assignm t hange of nam or domicile l tary cancellati n, and the registrati f licenses f use f the bove rights, b) Action f fai competi lon, protecti to th cons mer oppositions bservatio administrative Court cancellation, lity i fringemen gra i g f licenses, th ctio fo writ mand mu the protection f trad secrets and I gen ral th ci l, penal d dmi istr tive its rel ti g to those ghts actions d su ts instit d by m (us) against m (us) A d that in all th bove matt rs they may bstitute this Pow f Attorney ompromise conciliate admit the facts of the case desist cancel receive resig nd ratify cts d by represe t tive without power f ttorney

Give and igned this/Dad y firmad h y 28 Sept 1998

I /

Signature Ha ry H P n J Firma
Chi f Ex tiv Offi

29 MAR 2006

CAVELIER ABOGADOS
WI PODERE 181 (MINUTA N 121126 USA)

CERTIFICADO NOTARIAL (INDIVIDUO)

A los ___ días del mes d _____ de 19_____

an mi, Notario Publico de _____

comparecio(eron) personalmente _____

_____

q ie (es) doy fe d conoce y me const q es(son) l (s) persona(s) firmante(s) del documento que precede, y q lla(es) tiene(n) capacidad legal para otorgarlo

_____ N tario Público

NOTARIAL CERTIFICATE (INDIVIDUAL)

O this ___ day f _____ 19_____

before te Notary Public f _____

personally ppeared _____

_____

to m known, nd knowledge me (s) who executed that foregoing instrument and (he/she/they) have) legal capacity to execute it.

29 MAR 2006

Notary Public _____

CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy 26 de Septiembre de 19 98

compareció(ron) te mí

Harry H Penner Jr

q le (s) co ozco personalmente y q firma( ) este documento representació de la Sociedad/compañía

d nominad NEUROGEN CORPORATION

_____

Certifico:

1 Q los listo los ig ie tes doc me tos Certificado de la Constitución de Neurogen Corporation fechado 31 Mayo 1994 en Branford Connecticut

2 Qu dichos documentos prueban lo siguiente

2.1 Qu NEUROGEN CORPORATION es na Sociedad/Compañía legalmente constituída y existe te de acu rd co las leyes de Delaware

_____

2.2 Que l domicilio de dicha Sociedad/Compañía es 35 Northeast Industrial Road, Branford Connecticut, Estados Unidos de América.

2.3 Q l bjet bjet para los cu les se rga l prese te pod está comprendidos d tro d l bjeto social d la mencionad Sociedad/C mpañía

2.4 Q l(los) Sr (Sres) Harry H Penner

_____

tá( ) rizad (s) para torgar l p es Pod

C d d Branford

Es d Connecticut

H y 28 Sep d 19 98

NOTARIAL CERTIFICATE (CORPORATION)

On this 28th day of September 19 98

ppeared before me

Harry H. Penner Jr

who(m) I know personally and who(m) signed this document as represent tive(s) of the Corporation/Company named NEUROGEN CORPORATION

_____

I C rtify

1 Tha I have see th following documents.

Certificate of incorporation of Neurogen Corporation dated May 31, 1994 - Branford Connecticut

2 Tha h bove document d ly prove he foll wing:

2.1 That NEUROGEN CORPORATION is Corporation/Compa y legally constit ted and in xistence in accorda ce with the law f Delaware,

_____

2.2 Tha the domicile f said Corpora ion/Company is 35 Northeast Industrial Road, Branford Connecticut, United States of America.

2.3 That the p rpose f pu poses fo which he prese t Powe f Att ney is granted are comprised w hin th corporate purpose t forth he charte f th mentioned C rporatio /Company

2.4 That Mr (Messrs.) Harry H. Penner Jr.

_____

is(are) l orized to g h prese l we f Att

C ty Branford

Sta Connecticut

This 28th day f Sept , 98

TRADUCCION No 01 12 98

MARIA E V M ÉLEZ
Traductor Inglés Español
Licenciado
Res. No. 2879 Minister Justicia

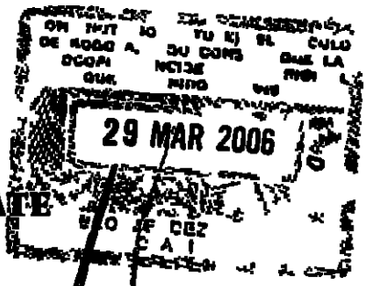
Notario Público ___ N tary Public

My Commission Expires April 30, 2006

L d m tos d be ld tificarse o f l y g

Docum ts must be id tified with date nd sig

J



STATE OF CONNECTICUT
OFFICE OF THE SECRETARY OF THE STATE

I **MILES S RAPOPORT** Secretary of the State of Connecticut and keeper of the seal thereof

DO HEREBY CERTIFY that JACQUELINE M GILMORE was duly appointed and commissioned a NOTARY PUBLIC in and for the State of Connecticut for the term of April 23 1998 to April 30 2003

and that to his/her acts and attestations as such full faith and credit are and ought to be given in and out of Court

In Testimony Whereof I have hereunto set my hand and affixed the Great Seal of the State of Connecticut at Hartford on **October 2 1998**

Miles S Rapoport

Secretary of the State



TRADUCCION N 01219 8
V P M PTELO
I rpr te Off I
gles Español I glés
N 2879 M J H

6

CONSULADO DE COLOMBIA
WASHINGTON D C

No. 2730

TRADUCCION N 01/2198
A MARTELO
I re Ofi I I
n Esp R I I gles
N 2879 Mi Justicia

EL CONSULADO DE COLOMBIA

CERTIFICA

Que es auténtica la firma de Fernesia Crawford

quien el día 07 de Octubre, 1998

desempeñaba las funciones de ofic aut. Depto Estado

la cual aparece al pie de los documentos anexos relacionados con Poder, representación y autenticado notarial

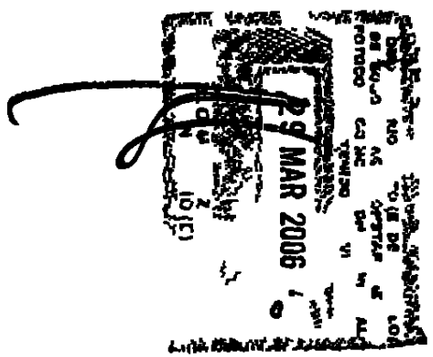
Dado en Washington D.C. a los Siete (07) días del mes de Octubre mil novecientos noventa y ocho (1998)

Pagado Impuesto de Timbre 6=
Pagado Derecho Consular 15=
Total 21=

(El Consulado no asume ninguna responsabilidad por el contenido de los documentos anexos)

SANDRA L GALVIS PINZON
Vi econsul

29 MAR 2006



MINISTERIO DE RELACIONES EXTERIORES

199920

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

98 DEC PM 12 10

JEFE DE LEGALIZACIONES SANTAFE DE BOGOTA D.C.



2

No 9900156 5

United States of America

DEPARTMENT OF STATE

To all to whom these presents shall come Greetings:

I Certify That the document hereunto annexed is under the Seal of the Secretary of State of the State of Connecticut and that such Seal is entitled to full faith and credit

29 MAR 2006

TRADUCCION N

MAR A ELV RA M RTEL PAL O N

Trad cto I te rete Oficial

Inglé Españ l I glés

Res N 2879 M Justicia

In testimony whereof I Strobe Talbott Acting Secretary of State have hereunto caused the seal of the Department of State to be affixed and my name subscribed by the Authentication Officer of the said Department at the city of Washington in the District of Columb a this seventh day of October 1998

Strobe Talbott

Acting Secretary of State

By Theresa D Crawford

Assistant Authentication Officer
Department of State

Issued pursuant to CHXI State of Sept. 5, 89, Stat. 68-69 22 USC 2657 22 USC 265 USC 30 28 USE 733 et. seq. 8 USC 443(f); RULE 44 Federal Rules of Civil Procedure.

FOR THE CONTENTS OF THE ANNEXED DOCUMENT THE DEPARTMENT ASSUMES NO RESPONSIBILITY

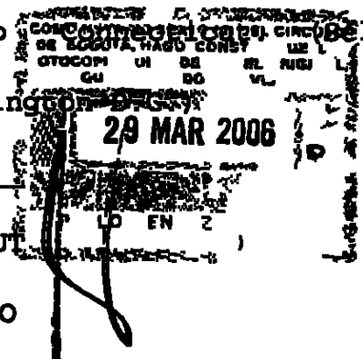
This certificate is not valid if it is removed or altered in any way whatsoever

TRADUCCIÓN OFICIAL No 01 12/98 preparada por María Elvira Martelo Traductora Oficial debidamente aprobada por el Ministerio de Justicia de Colombia por Resolución 2879 de 1995 y reconocida por el Ministerio de Relac ones Exteriores

---

(A continuación se traducen los sellos y legalizaciones de un documento escrito en inglés y español por el cual **NEUROGEN CORPORATION** otorga poder a **EMILIO FERRERO GONZALO PERDOMO LUZ CLEMENCIA DE PAEZ y GERMAN CAVELIER**) Dado y firmado el 28 de septiembre de 1998 (Firma ilegible) Harry H Penner Jr Pres dente Ejecutivo

CERTIFICADO NOTARIAL (SOCIEDAD) en inglés y español referente a la existencia legal de **NEUROGEN CORPORATION** expedido en la ciudad de Branford Estado de Connecticut el 28 de septiembre de 1998 (Firma ilegible) Notario Público (Sello notarial en tinta) Mi comisión expira el 30 de abril del 2003 (Sello en relieve) JACQUELINE M GILMORE Notario Público (Sello parcial del Consulado de Colombia en Washington D.C.)



ESTADO DE CONNECTICUT)

SECRETARÍA DE ESTADO

Yo MILES RAPAPORT Secretario del Estado de Connecticut y Custodio del sello del mismo **POR EL PRESENTE CERTIFICO QUE** JACQUELINE M GILMORE fue debidamente nombrada y comisionada como **NOTARIO PÚBLICO** en y para el Estado de Connecticut por el término 23 de abril de 1998 a 30 de abril del 2003

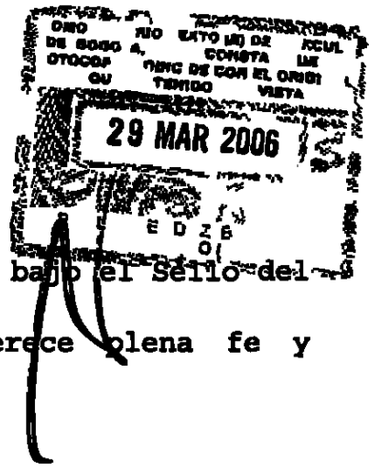
y que sus actos y declaraciones en calidad de tal merecen plena fe y crédito en los tribunales de justicia y fuera de ellos

EN FE DE LO CUAL he firmado y estampado el Gran Sello del Estado de Connecticut en Hartford el 2 de octubre de 1998 (Firma) Miles S Rapaport Secretario de Estado (Sello de oblea dorado del Estado de Connecticut)

No 9900156 5

ESTADOS UNIDOS DE AMÉRICA

DEPARTAMENTO DE ESTADO



A todos a quienes los presentes llegaren Salud

Certifico que el documento adjunto se encuentra bajo el Sello del Estado de Connecticut y que dicho sello merece plena fe y créd to

En fe de lo cual yo Strobe Talbott Secretario de Estado Encargado he hecho imponer el sello del Departamento de Estado y suscribir mi nombre por el Funcionario de Autenticaciones de dicho Departamento en la ciudad de Washington en el Distrito de Columbia hoy 7 de octubre de 1998

(Firma)Strobe Talbott Secretario de Estado Encargado

Por (Firma ilegible) Funcionario de Autenticaciones Asistente Departamento de Estado

El departamento no asume responsabilidad por el contenido del documento adjunto

Este certificado no es válido si sufre alguna eliminación o alteración

10

(Sello impreso del Departamento de Estado)

(Sello del Consulado de Colombia en Washington)

(En español) Certificación de la firma que antecede expedida por el Consulado de Colombia en Washington D C el día 7 de octubre de 1998 bajo el No 2730 Firmado por SANDRA L GALVIS PINZON Vicecónsul Pagados impuestos de timbre y derechos consulares

(Sello consular en tinta)

(Al dorso) Legalización de la firma que antecede expedida por el **MINISTERIO DE RELACIONES EXTERIORES** bajo el No 199920 del 1 de **diciembre de 1998** firmado por el Jefe de Legalizaciones

29 MAR 2006

Es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación

TRADUCCION No. 0112198
MARIA ELVIRA MARTELO
Traductora Intérprete Oficial
Inglés Español Inglés
Res. No. 2879 Min. Justicia

COLO 10611 801 003 7

Id 30

Dic 4/98

NO SE ASUME RESPONSABILIDAD DEL TEXTO

98 DEC 7 PM 2 08

JEFE DE LEGALIZACIONES
MINISTERIO DE RELACIONES EXTERIORES
BOGOTA D.C.

COMO NOTARIO SEXTO DEL CIRCULO DE SANTA
BOGOTA, HAGO CONSTAR QUE LA SI FIRM
Maria Martelo
COINCIDE(N) CON LA FIRMA REGISTRADA POR
LLOS) EN ESTA NOTARIA
SANTAFE DE

PABLO MENDEZ BARAJAS

MINISTERIO DE RELACIONES EXTERIORES
14209114
CUYA FIRMA APARECE
DOCUMENTO
SELLO
INSULAR

11

12420
3682

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1 COUNTRY UNITED STATES OF AMERICA

2 THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY
SUSAN CHWAT MYERS

3 ACTING IN THE CAPACITY OF
NOTARY PUBLIC OF NEW JERSEY

4 BEARS THE SEAL/STAMP OF
SUSAN CHWAT MYERS NOTARY

CERTIFIED

5 AT TRENTON NEW JERSEY

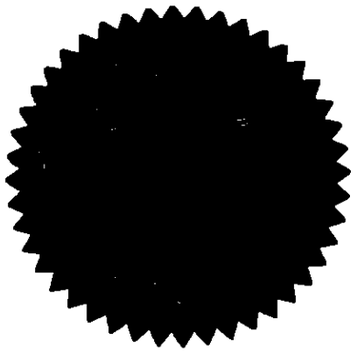
6 THE 13TH DAY OF AUGUST 2001

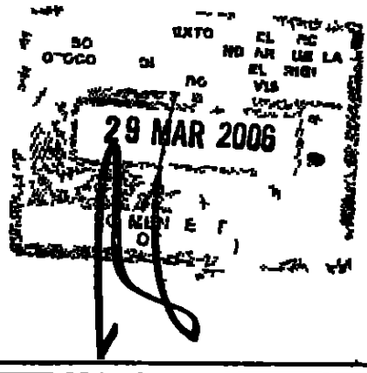
7 BY Peter R Lawrance NEW JERSEY TREASURER

8 NO A137024

9 SEAL/STAMP

10 SIGNATURE





12

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a 2-35
BOGOTA, COLOMBIA

181

Represe tación y Poder con autenticación notarial y Apostille para patentes modelos de tilidad diseños industriales marcas de fáb ica nombres comerciales ensenas nombres de dominio lemas comerciales licencias

Rep esentation and Power-of Attorney with notar al thent cat on and Apostille for patents utility models industrial designs t ademarks commercial names t de emblems domain names slogans licenses

REPRESENTACION Y PODER

REPRESENTATION AND POWER-OF-ATTORNEY

Y (nosotros) baj firmado ( )/I (we) the undersigned

~~AVENTIS PHARMACEUTICALS INC~~

domi liado ( ) n/ 300 Somerset Corporate Bl d

Bridgewater ~~, New Jersey 08807 , USA~~

EXITO (E) DEL INC LO
BOGOTA, ABO CONSTAR UE LA
COINCID CON EL ORIGIN
TENIDO VISTA
29 MAR 2006

po l prese te mbramo EMILIO FERRERO tpa. 31929 GONZALO PERDOMO pa 831 LUZ CLEMENCIA DE PAEZ tpa. 23555 y GERMAN CAVELIER, pa. 832 domi liados l Carrera 4 N 72 35 B gotá, Col mb a, bedec miento l d puesto l parágrafo 1 del Artic l 543 del Cód go de Comercio l primero como prin pal y l demás omo uple tes, en rden como mis (uestros) represe tantes en todos los asu tos d prop edad ndustrial con fac ltad para rec b notif cac es y nombrar poderados judic ales extrajud l El primer representante plente reemplazará l princ pal en caso d ausenc mped mento temporal defin vo d aq él L misma regl se apl cará and l seg ndo representante plente haya d reemplazar l primero l tercero l seg ndo E tales casos, l representante prin pal l pr mero segundo plente en su aso ambos, declararán te ón de no jercer l representacion mediante declarac ó ten ad por Notar Públ co en C lombia, por Notari otro Func onari Públ co Cón l de Colombia, l tranjero y se ratare de mped men con l ce ficado respec vo S algun d los ombrado faltare def amente l g te tomará lugar Cuando cesare l usencia mped me to d l representante princ pal de primero seg ndo supl te en caso podrán ejercer l represe tac on en orden uno tros según l aso asumiéndol po l sol hecho d j rcerla, sand en ese momento l jerc de la represe tac ó por l primero seg ndo tercer suplente en su aso. Ad más f ero (confenmos) pode los b gados arriba ombrados para bte l protec ó d mi (uestra) prop edad nd str l y contra la competen desleal yo f to autorizo (amos) los d hos apoderados pura que me (os) represente an ualesq era en idades perso as, jerzan jurisd cc ón especialme te ante las d l orden admi istrat co tenc so admi stra vo y judicial así omo los trib nales de arb tramento en odo l ncern te l iguientes asu tos) Obten ó de patentes de enc ón mod los d lidad y d seño nd strales l reg stro de marcas de fábrica, colec vas def ns as de servic lemas merc les mbres omerciales nseñas ombre d domi ariedad egetales y denominac es d gen re vac ó traspaso, camb de ombre domi lio ncela- ón voluntaria, y l reg tro d l ce as d uso de esos derechos b) Las acciones d competencia desleal protecc ón d l consumidor posi ones observac on ncelac ó admi strativa y jud l lidad medidas autelares conces ón d l nc as, l tutela, la protecc ón de secretos nd les y general los j ic os viles pen les adm stra vos con nc oso admi stra vos relac onado con

due compl ance w h the terms f paragraph 1 f art le 543 f th C mmerc l Code d hereby appo EMILIO FERRERO tpa. 31929 GONZALO PERDOMO tpa. 831 LUZ CLEMENCIA DE PAEZ tpa. 23555 and GERMAN CAVELIER, tpa. 832 domic led at Carrera 4 N° 72 35 Bogotá Colomb a, th first as princ pal and the others as alternates the order f the appo tmen as ur representatives fo ll ndustrial property matters wi h fac l y to rece ve notif ca ons and to appoi attorneys in and o f Court. The first alternate shall replace the prin pal case f h absence f temporal or defini ve mped ment. The same rul w ll apply when the sec nd alternate representat ve to replace the firs one when th th rd to replace the f rst or second lternates in the turn both f them, second l such cases the princ pal represe tat ve or the first or second alternates the m or b th f them, shall tate he intenti not to act as representat ves through declaration g ve before Notary P bl C lombia, or before Notary or another P bl Off ial or C lombian Consul abroad and case f mped me th appropriat cert ficate shall uff ce If any f th appoi tees were to be d f tely absen the foll wing lternate shall take h place Wh he absenc mpedimen f the princ pal representat ve, f the f rs or second alternate in the turn cease the representat on can be taken again in their sequence by the pr nc pal th f rst second lternate depending on case and th mere fac or ts exerc se w ll ff ce The xerc se f the representation by the f rst, second th rd lternates in th turn hall end at h time l add we gran Power f Attorn y in favo f th above amed attorn ys l w so hat they may btai the protec on f my (ur) ndustri l property and again th unf compet on for wh h p rpose I (we) auth rize he said ttorneys to represent me (us) before any author es or persons with or witho t jurisdic on specially those admi stra ve admi strative conte tious and judicial as well as before Arb tral C urt in ll matters oncerning the following) Obtai me f paten l y model and ind strial designs the registra on f trademarks, llec ve def ns ve and servi marks, l gans commerc l name trad emblems, doma names vegetal varieties and denominat on f gin ts renewal ass gnmen change f name domi l vol tary cancellati and the registrat f l censes f use f th above rights b) Act ns f unfa competi on protect to he onsume ppos ons or bservat ons admi istra ve or Court cancellation ll ty infringeme gran ing f licenses, the action for wri mandamus, the protec f trade secre and in general the vil pen l and admi stra ve su ts relat ng to those ghts actions and su ts

esto derechos acc ones y procesos que promovamos se nos promuevan Y para que en todos los asuntos arriba determ ados, puedan sustitu este mand to tran gr con l ar admiti los hechos d l proceso des sti cancel rec b renunc ar y rat ficar los acto d agentes f osos.

nstituted by me ( ) or aga nst me (us). And that ll the bove matters they may bstitute th Power f Attorney compromise conc l te adinu th facts f he case, desist, cancel rece ve, res gn and rat fy acts d y representat ves wi hout power f ttorney

Dad y f rmad hoy/Given and gned h 8th day of AUGUST 2001

en/in Bridgewater, New Jersey USA

por/by Assistant Secretary

F rma _____ S gn ture

ROSS J OEHLER



© CAVELIER ABOGADOS

CERTIFICADO NOTARIAL (INDIVIDUO)

A los _____ días del mes de _____
de 200___ ante mí N tario Publ Funcionario A torizado
de _____
mparec ó(ro) pers nalmente _____

quien( ) doy fe de conocer y me nsta que es(so) la( ) pers na( ) firmante( ) del docume to que pre ede y quien(es) tiene( ) capacidad legal para torgarl

_____Notar o P bl Func onari A torizado N tary P bl Attest ng Of l_____

NOTARIAL CERTIFICATE (INDIVIDUAL) 13

On this _____ day f _____
200___ before me N tary Publi or Attesting Official f___
_____
personally ppeared _____

to me known, and known to me to be the person( ) who xec ted tha foregoing document, and who has(have) l gal capac ty to execute t.

CERTIFICADO NOTARIAL (SOCIEDAD)

H y 8 de AGOSTO de 200 1
C mparec o(ro) ante mí
ROSS J. OEHLER
q n(es) nozc personalmente y que firma(n) este docume representac ón de la Sociedad/ ompañía denominada AVENTIS PHARMACEUTICALS INC

Certific

1 Q he isto l g entes documentos
ARTICULOS DE CONSTITUCION 7/9/1964 EXPEDIDOS EN EL ESTADO DE DELAWARE EEUU
RESOLUCION DE LA JUNTA DIRECTIVA 2/28/1994 CONFIRIDO EN LA CIUDAD DE KANSAS MISSOURI
2 Que d hos documentos prueban lo siguiente

2 1 Que AVENTIS PHARMACEUTICALS INC

una S dad/Compañía l galmente onstituida y existe te de acuerdo on las leyes de Estado de Delaware Estados Unidos de America

2 2 Que l domicilio de dicha Soc edad/Compañía es
300 Somerset Corporate Blvd
Bridgewater New Jersey 08807 USA

2 3 Que l bj to bjetos para los uales se torga l prese t pode está omprendidos dentro del bjeto oc l de la menc onada Soc edad/Compania

2 4 Que l(l) S (Sres) ROSS J OEHLER
esta( ) torizado( ) para torgar l presente Pode

C udad BRIDGEWATER
Estado NEW JERSEY EEUU

H y 8 AGOSTO de 200 1

NOTARIAL CERTIFICATE (CORPORATION)

O thi 8th day f AUGUST 200 1.
ppeared before me
ROSS J. OEHLER
who(m) I know personally and who(m) signed thi document as representative( ) f the Corporation/Company named _____
AVENTIS PHARMACEUTICALS INC

I certify

1 That I have seen the f llowing documents
Articles of Incorporation 7/9/1964 issued in State of Delaware USA
Resolution of Board of Directors 2/28/199 granted in Kansas City Missouri
2 That the bove docume ts duly prove the f llowing

2 1 That AVENTIS PHARMACEUTICALS INC

is Corporation/Company l gally onstituted and in existenc in accordanc with the laws of State of Delaware United States of Ameri

2 2 That the domicile f said Corporation/Comp y is
300 Somerset Corporate Blvd
Bridgewater New Jersey 08807 USA

2 3 That the purpose or purposes for which the present P we f Attorney is granted are orized within the corporation purposes se f rth in the harte f the mentioned C rporation/C mpany

2 4 That Mr (Messrs) ROSS J OEHLER
is(are) thorized to grant the present P we f Attorney

C ty Bridgewater
State New Jersey USA

Thi 8th day f AUGUST 200 1

_____N tari P bl Fun onari A t rizado – N tary P bl or Att ting Of c l___ _____

Los doc mentos deben iden f carse con fecha y gen

Doc ments must be iden fied w th date nd origin

SUSAN CHANT-MYERS
Notary Public
State of New Jersey
My Commission Expires Jun 8, 2006

CAVELIER ABOGADOS
WPPODE01 181 (MINUT N°12 1 1.2 6 USA)

APOSTILLE

(C tl de La H y d 5 oct b e 1961)

1 C try
This public do ument
2 has been gn d by
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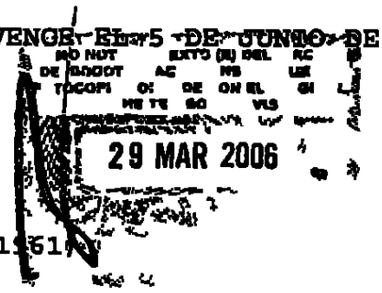
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TRADUCCIÓN OFICIAL 099/2001 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPANOL REALIZADA POR EDUARDO CALADO NOGUERA TRADUCTOR OFICIAL APROBADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 POR EL MINISTERIO DE JUSTICIA Y DEBIDAMENTE REGISTRADO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE LA REPÚBLICA DE COLOMBIA Y MEDIANTE EL CUAL AVENTIS PHARMACEUTICALS INC EMPRESA DOMICILIADA EN 300 SOMERSET CORPORATE BLVD BRIDGEWATER NEW JERSEY 08807 UNIDOS DE AMÉRICA OTORGA PODER A EMILIO FERRERO TPA 31929 GONZALO PERDOMO TPA 831 LUZ CLEMENCIA DE PAEZ TPA 23555 Y A GERMÁN CAVELIER TPA 832 EXPEDIDO Y FIRMADO EL OCHO DE AGOSTO DE 2001 EN BRIDGEWATER NEW JERSEY ESTADOS UNIDOS DE AMERICA POR EL SUBSECRETARIO FIRMADO ROSS J OEHLER

CERTIFICADO NOTARIAL EN INGLES Y EN ESPAÑOL POR EL CUAL SE CERTIFICA LA COMPARECENCIA DE ROSS J OEHLER PARA FIRMAR EL PODER ARRIBA CITADO A NOMBRE DE AVENTIS PHARMACEUTICALS INC Y PARA CERTIFICAR LA EXISTENCIA LEGAL EL DOMICILIO DE DICHA EMPRESA (300 SOMERSET CORPORATE BLVD BRIDGEWATER NEW JERSEY 08807 USA) Y LA CAPACIDAD DE ROSS J OEHLER PARA COMPROMETER A DICHA FIRMA BRIDGEWATER NEW JERSEY EEUU 8 DE AGOSTO DE 2001

Firmado SUSAN CHWAT MYERS SELLO SUSAN CHWAT MYERS NOTARIO PÚBLICO ESTADO DE NUEVA JERSEY MI CARGO VENCE EL 5 DE JUNIO DE 2006



APOSTILLA

(Convenc ón de La Haya del 5 de octubre de 1961)

1 Estados Unidos de Amér ca

Este documento públ co

2 ha s do f rmado por SUSAN CHWAT MYERS

3 qu en actúa en su cal dad de NOTARIO PÚBLICO DE NEW JERSEY

4 lleva el sello de SUSAN CHWAT MYERS NOTARIO

CERTIFICADO

5 en TRENTON NEW JERSEY

6 el 13 de agosto de 2001

7 por Peter R Lawrance tesorero de Nueva Jersey

8 Número A137024

9 Sello

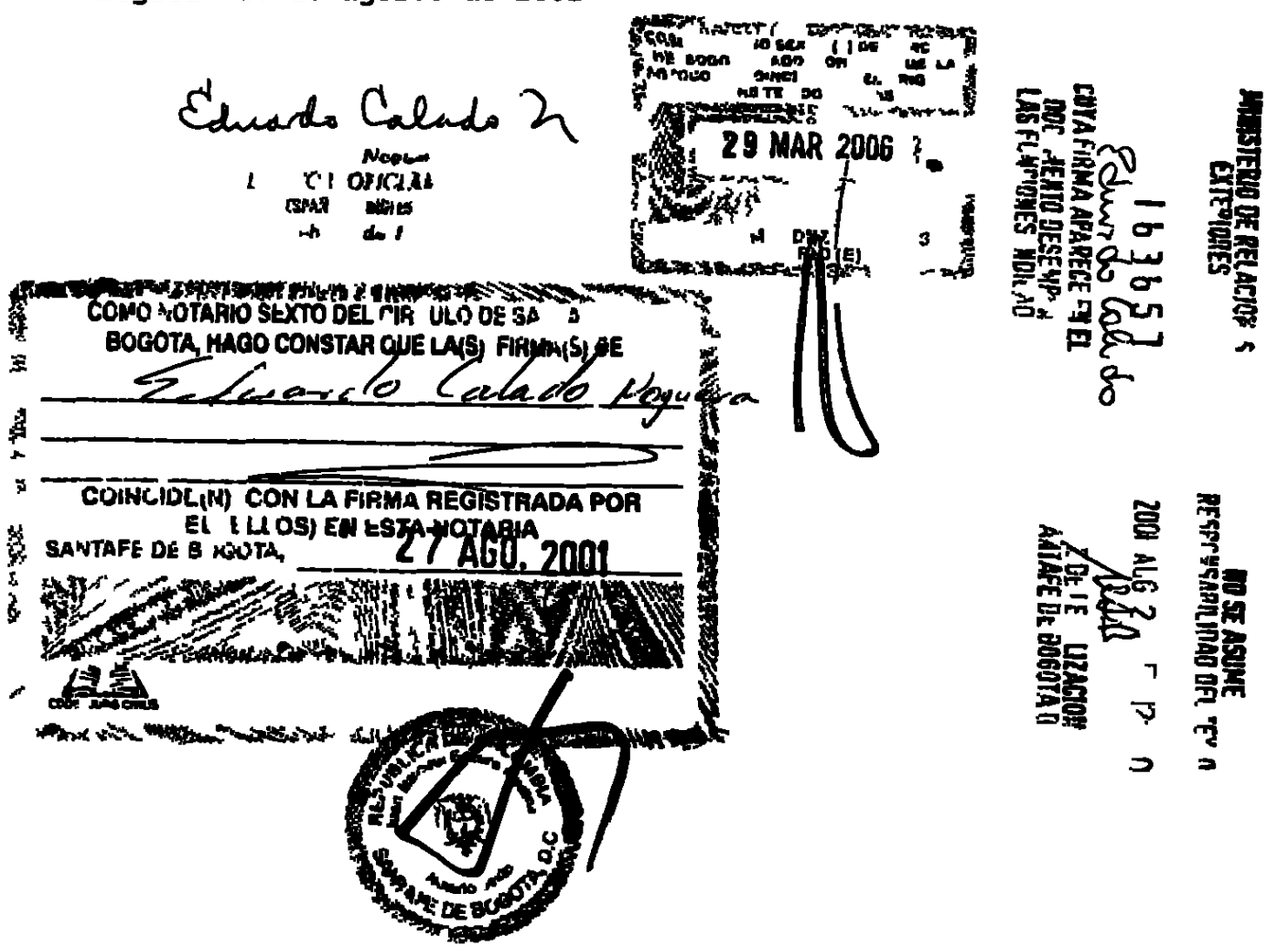
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WPCL002G ID 2615

Bogotá 27 de agosto de 2001



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DOCUMENTOS ANEXOS

1 ☒ Publicación Internacional WO 2005/023806 A2

2 ☒ **Forma PCT/ISA/210** Informe de Busqueda Internacional

3 ☒Extracto de publicación

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Declaration under Rule 4.17
— *of inventorship (Rule 4.17(iv)) for US only*

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

WO 2005/023806 A2

(54) Title: HETEROARYL FUSED PYRIDINES, PYRAZINES AND PYRIMIDINES AS CRF1 RECEPTOR LIGANDS

(57) Abstract: Substituted heteroaryl fused pyridine, pyrazine, and pyrimidine compounds that act as selective modulators of CRF1 receptors are provided. These compounds are useful in the treatment of a number of CNS and peripheral disorders, particularly stress, anxiety, depression, cardiovascular disorders, and eating disorders. Methods of treatment of such disorders, and well as packaged pharmaceutical compositions are also provided. Compounds of the invention are also useful as probes for the localization of CRF receptors and standards in assays for CRF receptor binding. Methods of using the compounds, receptor localization studies are give

HETEROARYL FUSED PYRIDINES, PYRAZINES AND PYRIMIDINES AS CRF1 RECEPTOR LIGANDS

This application claims priority from U S Pro s onal Application serial number 60/500 414 filed on September 5 2003

FIELD OF THE INVENTION

The present invention relates to novel subst tuted heteroaryl fused pyridine, pyrazine, and pyr m dine compounds that bi d with h gh select vity nd/ or h gh affinity to CRF receptors (Corticotropin Releasing Factor Receptors) This invention also relates to pharmace tical compositio s comprising such compounds and to the use of such compounds n treatm nt of psychiatric d sorders and neurological diseases, incl ding major depression x ety related disorders, post tra matı stress d sorder s pranuclear palsy a d feed ng d sorders, as well as treatment of immunological card ovascular or heart related d seases and colo ic hypersensitivity associated w th psychopathological disturbance and stress Addit on lly this invention relates to the se such compounds as probes for the local zation of CRF receptors cells and t ssues Preferred CRF receptors are CRF1 receptors

BACKGROUND OF THE INVENTION

Corticotropin releas ng factor (CRF), a 41 amino acid peptide, is the primary physiolog cal regulator of proop omelanocortin (POMC) derived peptide secretion from the anterior pituitary gland In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system nd produces a wide spectrum of autonom c, electrophys ological a d beh ioral effects consistent w th a neurotransm tter or neuromodulator role in brain There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological psychological and immunological stressors

Clin cal data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression anxiety related disorders and feeding disorders A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson s disease Huntington s disease progressive supranuclear palsy and

amyotrophic lateral sclerosis as they relate to the dysfu ction of CRF neurons in the central nervous system

In affective disorder or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug free individuals. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF In addit on, there is a blunted adrenocorticotropin (ACTH) response to CRF (i v- administered) observed in depressed patients Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be nvol ed in the symptoms seen in human depress on There is also preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain

CRF has also been implicated in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models Preliminary studies us ng the putative CRF receptor antagonist α-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces anxiolytic like effects that are qualitatively similar to the benzodiazepines Neurochemical endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders Chlordiazepoxide attenuates the anxiogen c ffects of CRF in both the confl ct test and in the acoustic startle test in rats The benzodiazepine receptor antagonist Ro l5 1788 which was without behavioral activity alone n the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist FG 7142 enhanced the actions of CRF

CRF has also been implicated in the pathogenesis of certain immunological cardiovascular or heart-related diseases such as hypertension tachycardia and congestive heart failure stroke and osteoporos s, as well as in premature birth, psychosocial dwarfism stress-induced fever ulcer diarrhea, post-operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress

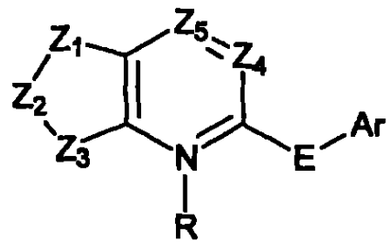
The mechanisms and sites of action through which conventional anxiolytics and antidepressants produce their therapeutic effects rema n to be fully elucidated It has been hypothesized however that they are involved in the suppression of CRF hypersecretion that is observed in these disorders Of particular i terest are that preliminary studies examining

the effects of a CRF receptor antagonist peptide (α helical CRF_{9-41}) a variety of behavioral paradigms have demonstrated that the CRF antagonist produces anxiolytic-like effects qualitatively similar to the benzodiazepines

SUMMARY OF THE INVENTION

The invention provides novel compounds of Formulae I (shown below), and pharmaceutical compositions comprising compounds of Formula I and at least one pharmaceutically acceptable carrier or excipient. Such compounds bind to cell surface receptors, preferably G-coupled protein receptors, especially CRF receptors (including CRF1 and CRF2 receptors) and most preferably CRF 1 receptors. Preferred compounds of the invention exhibit high affinity for CRF receptors, preferably CRF 1 receptors. Additionally preferred compounds of the invention also exhibit high specificity for CRF receptors (i.e. they exhibit high selectivity compared to their binding to non-CRF receptors). Preferably they exhibit high specificity for CRF 1 receptors.

Thus, in certain aspects, the invention provides compounds of Formula I-a



I-a

and the pharmaceutically acceptable salts thereof wherein

E is a single bond, O, $S(O)_m$, NR_{10} or $CR_{10}R_{11}$;

R_{10} and R_{11} are independently hydrogen or C_1-C_4 alkyl;

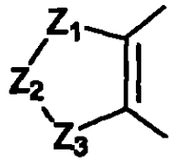
m is 0, 1 or 2;

Ar is chosen from

phenyl which is mono-, di- or tri-substituted; 1-naphthyl and 2-naphthyl each of which is optionally mono-, di- or tri-substituted; and optionally mono-, di- or tri-substituted heteroaryl; said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N, O and S;

R is oxygen or absent,

the group



represents a saturated, unsaturated or aromatic 5-membered ring system contain ng 0 or 1 heteroatoms, wherein

Z_1 is CR_1 or CR_1R_1

Z_2 is nitrogen, oxygen, sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen oxygen sulfur sulfoxide sulfone CR_3, or CR_3R_3

R is chosen from hydrogen, halogen, hydroxy cyano, amino optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy optionally substituted mono or dialkylamino, optionally substituted cycloalkyl optionally substituted (cycloalkyl)alkyl, optionally substituted alkylthio optionally substituted alkylsulfinyl, optionally substituted alkylsulfonyl, optionally substituted mono- or dialkylcarboxamide, optionally substituted carbocyclic aryl optionally substituted heterocycle and optionally substituted heteroaryl said optionally substituted heterocycle or heteroaryl ha ing from 1 to 3 rings 5 to 7 ring members in each ring and, in at least one of said rings from 1 to about 3 heteroatoms selected from the group consisting of N O and S

$R_{\_}$ and R_3 are independently chosen from hydrogen, halogen hydroxy amino cyano, nitro, alkyl haloalkyl alkoxy aminoalkyl hydroxyalkyl and mono and dialkylamino, wherein when R or R_1 is optionally substituted alkyl then R_3 is optionally substituted $C_{_3}$alkyl

R R_2 and R_3 are independently chosen from hydrogen, halogen, alkyl haloalkyl and aminoalkyl

R_2 is chosen from hydrogen, optionally substituted alkyl optionally substituted haloalkyl, and optionally substituted aminoalkyl

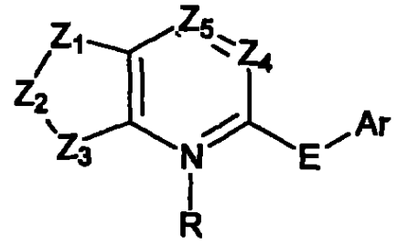
Z_4 is NR or CR_4

Z_5 is NR or CR_5

R_4 and R_5 are ndependently chosen from hydrogen, halogen, hydroxy amino cyano tro, optionally substituted alkyl optionally substituted alkenyl, optionally substituted alky yl, optionally substituted alkoxy optionally substituted mono or dialkylamino optionally substituted (cycloalkyl)alkyl optionally substituted alkylthio optionally

substituted alkylsulfinyl optionally substituted alkylsulfonyl optionally substituted mono- or dialkylcarboxamide optionally substituted carbocyclic aryl and optionally substituted heteroaryl said optionally substituted heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

In certain other aspects, the invention provides compounds of Formula I b



Formula I b

or a pharmaceutically acceptable salt thereof wherein

E is a single bond, O $S(O)_m$ NR_1 or $CR_{10}R_{11}$

R_1 and R are independently hydrogen or C_1-C_4 alkyl

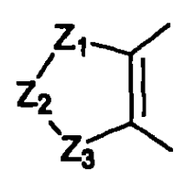
m is 0 1 or 2

R is oxygen or absent

Ar is chosen from

phenyl which is mono- di or tri-substituted 1 naphthyl and 2 naphthyl each of which is optionally mono- di or tri-substituted and optionally mono- di or tri-substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O, and S

the group



represents a saturated unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z_1 is CR_1 CR_1R_1 or NR_1

Z_2 is CR_2 or CR_2R_2

Z_3 is CR_3, CR_3R_3 or NR_3

R_1 and R_1 are chosen from hydrogen, C_1-C_{10}alkyl C_2-C $_0$alkenyl, C_2-C_{10}alkynyl C_3 C_7cycloalkyl (benzo)C_3-C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl, C_3-$_9$heterocycloalkyl, (C_{3-9}heterocycloalkyl)C_1-C_4alkyl, (benzo)C_{3-9}heterocycloalkyl, ((benzo)C_{3-9}heterocycloalkyl)C_1-C_4alkyl and halo(C_1-C_6)alkyl, each of which is substituted with 0 or more substituents independently chosen from halogen, hydroxy amino oxo cyano, C_1-C_6alkyl, C_1-C_6alkoxy haloC_1-C_6alkoxy C -C_6alkanoyl, C_1 C_6alkanoyloxy C_1-C_6alkoxycarbonyl N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N (C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino N-(C_1-C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino C_1-C_6alkylsulfonamide, C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C_1-C_6alkoxyC_1-C_6alkyl, C_1-C_6haloalkoxy 5 to 7 membered heteroaryl 5 to 7 membered heterocycloalkyl, mono- and di-(C_1-C_6)alkylamino, N (C -C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, mono- and di-(C_1 C_6)alkylcarbamoyl, XR_C and X Z, with the proviso that R and R_1 is not aryl or heteroaryl substituted alkyl

R_2 is hosen from hydrogen halogen hydroxy amino cyano nitro C -C_3alkyl halo(C C_3)alkyl C -C_3alkoxy amino(C_1-C_3)alkyl, and mono and di(C_1-C_6)alkylamino

R_3 is chosen from hydrogen, hydroxy amino, halogen cyano, nitro, C_1-C_3alkyl, halo(C_1 C_3)alkyl, C -C_3alkoxy amino(C_1-C_3)alkyl hydroxy(C -C)alkyl, cyano(C_1-C_3)alkyl and mono and di(C -C_3)alkylamino

R_3 is chosen from hydrogen, hydroxy amino C_1-C_3alkyl, halo(C -C)alkyl, C -C_3alkoxy amino(C_1-C_3)alkyl hydroxy(C_1-C_3)alkyl cyano(C_1-C_3)alkyl and mono and di(C_1 C_3)alkylamino

R_1 R_2 and R_3 are independently chosen from hydrogen, halogen C_1-C_6alkyl, halo(C_1 C_6)alkyl and amino(C_1-C_6)alkyl

Z_4 is NR or CR_4

Z_5 is NR or CR_5

R_4 and R_5 are independently chosen from hydrogen, halogen cyano, nitro, amino, mono or di(C_1-C_6carbhydryl)amino, C_1-C_6carbhydryl, (C_3-C_7cyclocarbhydryl)C_0-C_4carbhydryl -O(C_3-C_7cyclocarbhydryl), halo(C -C_6)carbhydryl -O(halo(C C_6)carbhydryl) -O(C -C_6carbhydryl) S(O)$_n$(C_1-C_6carbhydryl) and 4 to 7 membered heterocycloalkyl

where each carbhydryl is ndependently straight, branched o yclic, conta ns zero o 1 o more double o triple bonds, and is optionally substituted with one or more substituents independently chosen from halogen hydroxy amino, oxo, cyano C_1-C_4alkoxy and mono- and di(C_1-C_4)alkylamino,

and

where each C_3-C_7carbhydryl heterocycloalkyl is optionally substituted by one or more substituents independently chosen from halogen, amino, hydroxy oxo, cyano, C_1-C_4alkoxy and mono- a d di(C_1-C_4)alkylam no or

R_5 taken i combination with R_1 or R_1 forms a 5 9 membered heterocycl

R_A is independently selected at each occurrence from halogen cyano nitro halo(C_1-C_6)alkyl halo(C_1-C_6)alkoxy hydroxy m no, C -C_6alkyl substituted with 0-2 R_B C_2-C_6alkenyl substituted with 0-2 R_B, C_2-C_6alkynyl substituted with 0-2 R_B, C_3-C_7cycloalkyl substituted with 0-2 R_B, (C -C_7cycloalkyl)C_1-C_4alkyl substituted with 0 2 R_B, C -C_6alkoxy substituted with 0 2 R_B, NH(C_1 C_6alkyl) s bstituted w th 0 2 R_B, N(C_1-C_6alkyl)(C_1-C_6alkyl) each C -C_6alkyl mdependently subst tuted with 0 2 R XR_C and Y

R_B is mdependently selected at each occurrence from the group consist g of halogen, hydroxy cyano, amino, C -C_4alkyl -O(C -C_4alkyl) NH(C_1-C_4alkyl) N(C C_6alkyl)(C_1-C_4alkyl) S(O)$_n$(alkyl) halo(C -C_4)alkyl halo(C_1-C_4)alkoxy CO(C C_4alkyl) CONH(C -C_4alkyl) CON(C -C_4alkyl)(C -C_4alkyl) XR_C and Y

R_C and R_D, which may be the same or different, are independently selected at each occurrence from

hydrogen, and

stra ght, branched, or cyclic alkyl groups, incl ding (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, which straight, branched or cyclic alkyl groups conta1 zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy halogen cyano, amino, C_1-C_6alkoxy NH(C_1-C_6alkyl) N(C_1 C_6alkyl)(C_1-C_6alkyl), NHC(=O)(C -C_6alkyl) N(C_1-C_6alkyl)C(=O)(C_1-C_6alkyl), NHS(O)$_n$(C_1-C_6alkyl), S(O)$_n$(C -C_6alkyl), S(O)$_n$NH(C_1-C_6alkyl) S(O)$_n$N(C_1 C_6alkyl)(C_1-C_6alkyl) and Z

X is independently selected at each occurrence from the group consisting of -O- -C(=O)O- S(O)$_n$- NH NR_D- -C(=O)NH -C(=O)NR_D- S(O)$_n$NH -S(O) NR_D- -OC(=S)S-

NHC(=O)- $NR_DC(=O)$- $NHS(O)_n$ $-OSiH_2$- $-OSiH(C_1$-C_6alkyl)- $-OSi(C_1$-C_6alkyl)$(C_1$-C_4alkyl)- and $-NR_DS(O)_n$-

Y and Z are independently selected at each occurrence from 3 to 7 membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic which may be further substituted with one or more substituents independently selected from halogen, oxo hydroxy amino cyano, C_1-C_4alkyl, -O(C -C_4alkyl) NH(C -C_4alkyl) N(C -C_4alkyl)(C -C_4alkyl) -C(O)(C_1-C_6alkyl), and -$S(O)_n$(alkyl), wherein said 3- to 7-memberered heterocyclic groups contain one or more heteroatom(s) independently selected from N O and S, with the point of attachment being either carbon or nitrogen and

n is independently selected at each occurrence from 0 1 and 2

Certain preferred compounds of Form Ia I-a or Form Ia I b include those in which at least one of Z_4 and Z_5 is not NR. Certain other preferred compounds of Form Ia I-a or Formula I b include those in which Z_4 is selected from N and CR_4 and Z_5 s selected from N and CR_5

Certain preferred compounds of Formula I b include those ompounds in which Ar is chosen from phenyl which is mono- di or tri-substituted with R_A, and 1 naphthyl 2 naphthyl pyridyl pyrimidinyl, pyrazinyl, pyridizinyl, thienyl, thiazolyl oxazolyl, isoxazolyl, pyrrolyl furanyl and triazolyl each of which is optionally mono- di or tri substituted with R_A and

R_1 and R_1 are chosen from C_1-C_{10}alkyl C_2-C $_0$alkenyl, C_2-C $_0$alkynyl, C_3 C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl (benzo)C_3-C_7cycloalkyl (benzo)C_3-$_9$heterocycloalkyl ((benzo)C_{3-9}heterocycloalkyl)C_1-C_4alkyl and halo(C_1-C_6)alkyl, each of which is substituted with 0 1 2 or 3 substituents independently chosen from halogen hydroxy amino oxo cyano C -C_6alkyl C_1-C_6alkoxy haloC$_1$-C_6alkoxy C -C_6alkanoyl, C -C_6alkanoyloxy C_1 C_6alkoxycarbonyl N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, C_1-C_6alkylsulfonamide, C_1 C_6alkylsulfonyl C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C_1-C_6alkoxyC_1-C_6alkyl, C_1 C_6haloalkoxy 5 to 7 membered heteroaryl 5 to 7 membered heterocycloalkyl mono- and di (C_1-C_6)alkylam no N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkanoyloxy)-N-(C_0-

C_6alkyl)amino, N-(C_1-C_6alkoxycarbonyl)-N-(C_1-C_6alkyl)amino mono- and di-(C_1-C_6)alkylcarbamoyl XR_C and X Z.

As used herein the term Formula I" is generally intended to refer to compounds of either Formula I-a or Formula I b and subformulae thereof

The invention further comprises methods of treating patients suffering from certain disorders with therapeutically effective amount of at least one compound of the invention These disorders include CNS disorders, particularly affective disorders, anxiety disorders, stress-related disorders, eating disorders and substance abuse The patient suffering from these disorders may be a human or other animal (preferably a mammal), such as a domesticated companion animal (pet) or livestock animal Preferred compounds of the invention for such therapeutic purposes are those that antagonize the binding of CRF to CRF receptors (preferably CRF1 or less preferably CRF2 receptors) The ability of compounds to act as antagonists can be measured as an IC_{50} value as described below

According to yet another aspect, the present invention provides pharmaceutical compositions comprising compounds of Formula I or the pharmaceutically acceptable salts (by which term is also encompassed pharmaceutically acceptable solvates) thereof which compositions are useful for the treatment of the above-recited disorders The invention further provides methods of treating patients suffering from any of the above-recited disorders with an effective amount of a compound or composition of the invention

Additionally this invention relates to the use of the compounds of the invention (particularly labeled compounds of this invention) as probes for the localization of receptors in cells and tissues and as standards and reagents for use in determining the receptor-binding characteristics of test compounds

Preferred heteroaryl fused pyridine, pyrazine, and pyrimidine compounds of the invention exhibit good activity i.e a half maximal inhibitory concentration (IC_{50}) of less than 1 millimolar in a standard *in vitro* CRF receptor binding assay such as the assay provided in Example 51 which follows. Particularly preferred substituted heteroaryl fused pyridine, pyrazine, and pyrimidine compounds of the invention exhibit an IC_{50} of about 1 micromolar or less, still more preferably an IC_{50} of about 100 nanomolar or less even more preferably an IC_{50} of about 10 nanomolar or less Certain particularly preferred compounds of the invention will exhibit an IC_{50} of 1 nanomolar or less in such a defined standard *in vitro* CRF receptor binding assay

DETAILED DESCRIPTION OF THE INVENTION

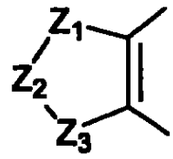
In addition to compounds of Formula I-a, described above, the invention is further directed to compounds and pharmaceutically acceptable salts of Formula I wherein

R is oxygen or absent;

Ar s chosen from

phenyl which is mono- di or tri-substituted with R_A and 1 naphthyl 2 naphthyl pyridyl, pyrimidinyl, pyrazinyl pyridizinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolyl, furanyl, and triazolyl, each of which is optionally mono- di or tri-substituted with R_A

the group



represents a saturated, unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z_1 is CR or CR_1R_1

Z_2 is nitrogen, oxygen, sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen oxygen, sulfur sulfoxide sulfone CR_3 or CR_3R_3

R_1 is chosen from

i) halogen, hydroxy cyano, amino C_1-C_6alkyl -O(C_1-C_6 alkyl) mono or di(C_1-C_6alkyl)amino, (C_3-C_7cycloalkyl)C_1-C_4alkyl, halo(C_1-C_6)alkyl, -O(halo(C_1-C_6)alkyl) and S(O)$_n$(C_1-C_6alkyl), -O(C_3-C_7cycloalkyl)C -C_4alkyl and S(O)$_n$(C_1-C_6alkyl),

where each alkyl s independently straight, branched or cycl c, contains zero or 1 or more double or triple bonds, and is optionally substituted with one o more substituents independently chosen from halogen hydroxy amino, oxo cyano, C_1 C_1 C_4alkoxy and mono- or di(C_1-C_4)alkylamino

and

where each C_3-C_7cycloalkyl is optionally substituted by one or more substituents ndependently chosen from halogen amino hydroxy oxo, cyano, C -C_4alkoxy and mono- or di(C_1-C_4)alkylamino, and

ii) phenyl which is mono- di or tri-substituted with R_A 1 naphthyl 2 naphthyl pyridyl dihydropyridyl tetrahydropyridyl, pyrimidinyl pyrazinyl pyr drzinyl thienyl thiazolyl oxazolyl isoxazolyl pyrrolyl furanyl, and triazolyl each of which is optionally mono- di or tri-substituted with R_A

R_2 and R_3 are independently chosen from hydrogen halogen hydroxy amino, cyano nitro C_1-C_3alkyl halo(C -C_3)alkyl C_1-C_3alkoxy amino(C_1-C_3)alkyl and mono and di(C_1 C_6)alkylam o

R_1 R_2 and R_3 are independently chosen from hydrogen, halogen, C -C_6alkyl halo(C C_6)alkyl and amino(C -C_6)alkyl

R_2 is chosen from hydrogen C -C_6alkyl halo(C -C_6)alkyl and am no(C -C_6)alkyl

Z_4 is NR or CR_4

Z_5 is NR o CR_5

R_4 and R_5 are independently chosen from hydrogen halogen cyano nitro amino mono o d (C_1-C_6carbhydryl)amino, C_1-C_6carbhydryl (C_3-C_7cyclocarbhydryl)C_0-C_4carbhydryl -O(C_3-C_7cyclocarbhydryl), halo(C_1-C_6)carbhydryl -O(halo(C_1 C_6)carbhydryl) -O(C_1-C_6carbhydryl), and S(O)$_n$(C_1-C_6carbhydryl),

where ea h carbhydryl is independently straight, branched, or cycl c, contai s zero or 1 or more double or triple bonds, and is option lly subst tuted with one or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano C_1 C_4alkoxy and mono- and di(C_1-C_4)alkylamino

and

where each C -C_7carbhydryl is opt onally substituted by one or more substituents independently chosen from halogen amino hydroxy oxo, cyano C -C_4alkoxy and mono- and di(C -C_4)alkylamino

R_A is independently selected at each occurrence from halogen, cyano, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino C_1-C_6alkyl substituted with 0-2 R_B, C_2-C_6alkenyl substituted with 0-2 R_B, C_2-C_6alkynyl substituted with 0-2 R_B C_3-C_7cycloalkyl substituted with 0-2 R_B, (C_3-C_7cycloalkyl) C_1-C_4alkyl substituted with 0-2 R_B, C_1-C_6alkoxy substituted with 0-2 R_B, NH(C_1-C_6alkyl) substituted with 0-2 R_B, N(C_1-C_6alkyl)(C_1-C_6alkyl) each C_1-C_6alkyl independently substituted with 0-2 R_B, XR_C and Y

R_B is independently selected at each occurrence from the group consisting of halogen, hydroxy cyano, amino, C_1-C_4alkyl -O(C_1-C_4alkyl), NH(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl) $S(O)_n$(alkyl), halo(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy CO(C_1-C_6alkyl), CONH(C_1-C_4alkyl) CON(C_1-C_4alkyl)(C_1-C_4alkyl) XR_C and Y

R_C and R_D, which may be the same or different, are independently selected at each occurrence from

hydrogen, and straight, branched, or cyclic alkyl groups, including (cycloalkyl)alkyl groups consisting of 1 to 8 carbon toms, which straight, branched, or cyclic alkyl groups contain zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms m y be further subst tuted with one or more substituent(s) ndependently selected from oxo hydroxy halogen, cyano, amino, C -C_6alkoxy NH(C -C_6alkyl) N(C_1-C_6alkyl)(C -C_6alkyl) NHC(=O)(C -C_6alkyl) N(C_1-C_6alkyl)C(=O)(C_1-C_6alkyl), $NHS(O)_n$(C_1-C_6alkyl), $-S(O)_n$(C_1-C_6alkyl) $S(O)_nNH$(C_1-C_6alkyl) $S(O)_nN$(C -C_6alkyl)(C_1-C_6alkyl) and Z

X is independently selected at each occurrence from the group consisting of $-CH_2$ $-CHR_D$- O- -C(=O)- -C(=O)O- $S(O)_n$ NH NR_D- -C(=O)NH -C(=O)NR_D- $S(O)_nNH$ $-S(O)_nNR_D$- -OC(=S)S NHC(=O) $NR_DC(=O)$- $NHS(O)_n$ $-OSiH_2$ -OSiH(C_1-C_4alkyl)- -OS (C_1-C_4alkyl)(C_1-C_4alkyl)- and $-NR_DS(O)_n$-

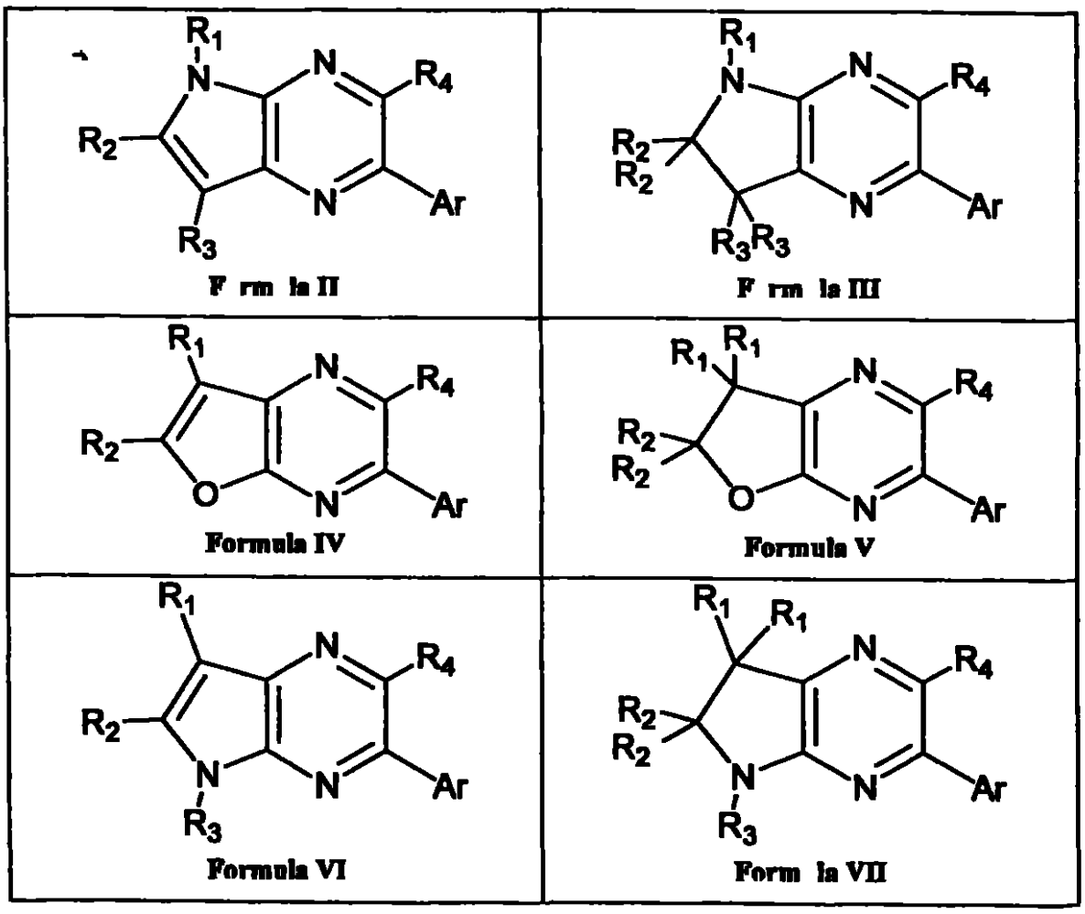
Y and Z are independently selected at each occurrence from 3 to 7 membered carbocyclic or heterocyclic groups which are saturated unsaturated or aromatic, which may be further substituted with one or more substituents ndependently selected from halogen, oxo, hydroxy amino, cyano C_1-C_4alkyl -O(C_1-C_4alkyl) NH(C_1-C_4alkyl), N(C C_4alkyl)(C_1-C_4alkyl) and $-S(O)_n$(alkyl),

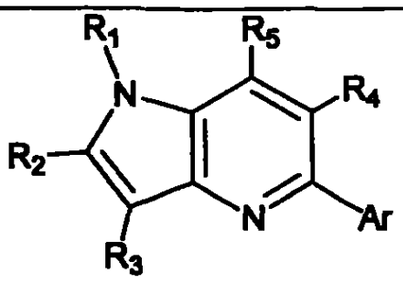
wherein said 3 to 7 memberered heterocyclic groups contain one or more heteroatom(s) independently selected from N O and S with the point of attachment being either carbon or n trogen and

n is independently selected at each occurrence from 0 1 and 2 Such compounds will be referred to as compounds of Formula I-c.

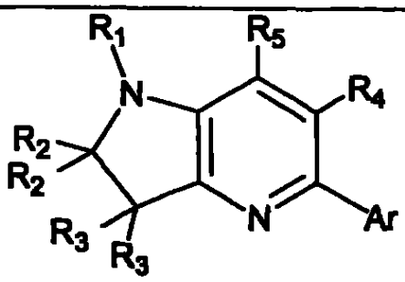
Certain preferred compounds of Formula I-c include those in which at least one of Z_4 and Z_5 is not NR Certain other preferred compounds of Formula I-c include those in which Z_4 is selected from N and CR_4 and Z_5 is selected from N and CR_5

Particular embodiments of the invention include compounds having the following Formula

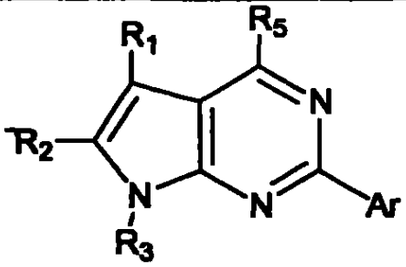




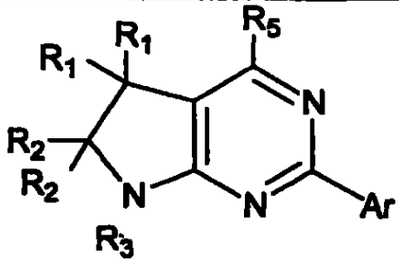
Formula VIII



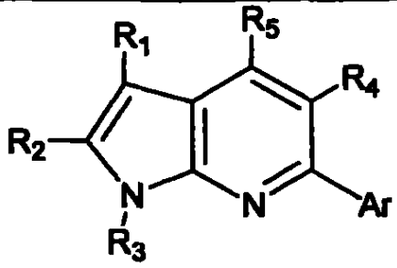
Formula IX



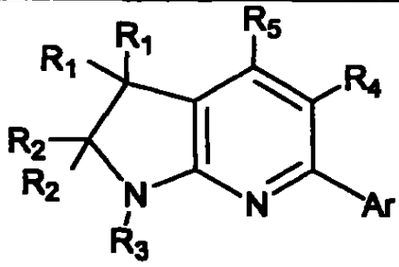
Formula X



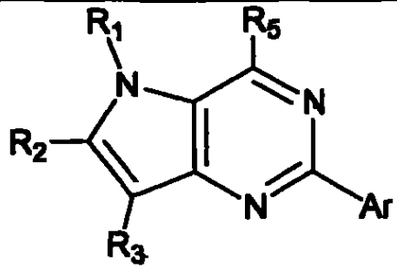
Formula XI



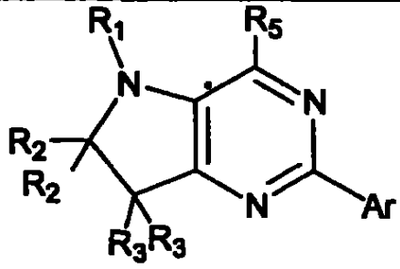
Formula XII



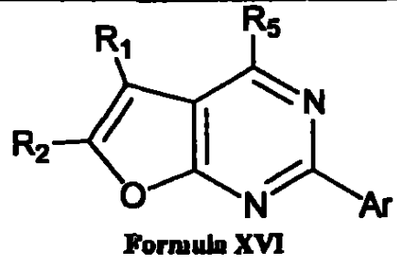
Formula XIII



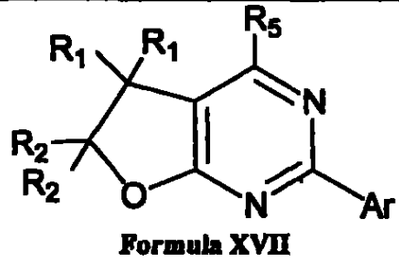
Formula XIV



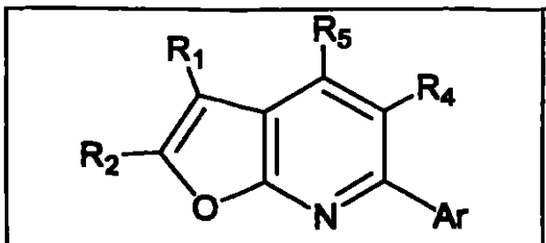
Formula XV



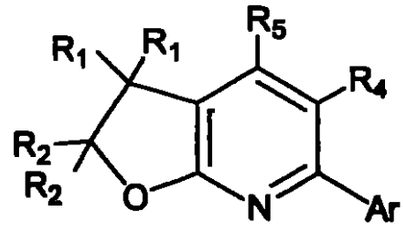
Formula XVI



Formula XVII



Formula XIII



Formula XIX

For each of the compounds and salts of Formul II Formula XIX, R_1 R_1 R_1 R_2 R_2 R_2 R_3, R_3 R_3 R_4, R_5, and Ar are as defined above for Formula I or preferably are as defined above fo Formula I-a, I b, or I-c

More prefereably

R_1 R and R are as def ned for Form I I-a, I b, or I-c

R_2 and R_3 re hydrogen

R_2 (or R_2") is selected from hydrogen methyl and ethyl

R_3 (or R_3") is selected from hydrogen and C -C_6alkyl (or more preferably R_3 o R_3 s C_1 C_3alkyl when Z s NR or whe Z s NR_3

R_4 and R_5 are independently selected from hydrogen halogen cyano am no, C -C_6alkyl C C_6alkoxy C -C_7cycloalkyl (C_3-C_7cycloalkyl)C -C_4alkyl (C_3-C_7cycloalkyl)C C_4alkoxy mono and di(C -C_6alkyl)amino, amino(C_1-C_6)alkyl mono and d (C C_6alkyl)amino(C -C_6)alkyl halo(C_1-C_6)alkyl and halo(C_1-C_6)alkoxy and

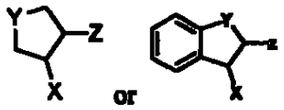
Ar is selected from the group consisting of phenyl, pyridyl and pyrimid nyl each of which is mono- d or trisubst tuted with substituents independe tly chose from halogen cya o, nitro, halo(C_1-C_6)alkyl halo(C_1-C_6)alkoxy hydroxy mino, C_1-C_6alkyl C_2-C_6alkenyl C_2-C_6alkynyl C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C_1-C_4alkyl C -C_6alkoxy mono- and d (C_1-C_6alkyl)am no amino(C_1-C_6)alkyl and mono- nd di(C_1-C_6alkyl)amino wherem, in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula II Formula XX above, is substituted

In certain preferred compounds of Form I I (e g I-a and I b) nd arious subformulae thereof wh ch comprise a R or R_1 group the R_1 or R_1 residue is selected from C_1-C_{10}alkyl and (C_3-C_7cycloalkyl)C_0-C_4alkyl each of which is substituted with 0 or

more substituents independently chosen from halogen hydroxy amino oxo cyano, C_1-C_4alkoxy and mono- and di-(C -C_4)alkylamino

In certain other preferred compounds of Formula I (e g I-a and I-b) and various subformulae thereof which comprise a R or R_1 group, the R_1 or R_1 residue is selected from C_{3-9}heterocycloalkyl and (C_{3-9}heterocycloalkyl)C_{1-4}alkyl each of which is substituted with 0-4 substitutents selected from halogen, amino, hydroxy nitro cyano, C_1-C_6alkyl C C_6alkoxy C_1-C_6hydroxyalkyl C_1-C_6alkoxyC_1-C_6alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy mono- and di-(C_1-C_6)alkylamino XR_C Certain preferred C_{3-9}heterocycloalkyl and (C_{3-9}heterocycloalkyl)C -$_4$alkyl groups include those chosen from tetrahydrofuranyl tetrahydropyranyl, morpholinyl pyrrolidinyl piperidinyl piperazinyl [2 2 1]-azabicyclic rings, [2 2.2]-azabicyclic rings, [3.3 1]-azabicyclic rings quinuclidinyl azetidinyl azet d onyl oxindolyl dihydro midazolyl, and pyrrol d nonyl each of which is subst tuted with from 0 to 2 substituents independently chosen from (i) halogen, hydroxy amino cyano or (ii) C -C_4alkyl, C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino, each of which is subst tuted with 0 or 1 subst tuents selected from halogen hydroxy amino, C -$_2$alkoxy or C_{3-} heterocycloalkyl

Certain other preferred compounds of Formula I (e g I-a or I-b) and ompounds of Formulae II XIX include those compounds in wh ch R_1 or R is selected from 3-pentyl 2 butyl 1 methoxy but 2 yl 1-dimethylamino-but 2 yl, 3-(thiazol 2 yl)-1*H*-pyrazol 1 yl, and groups of formula



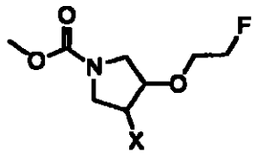
wherein X is the point of attachment to the nitrogen of the imidazo ring,

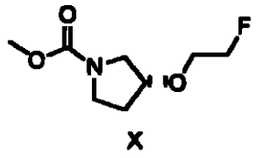
Y is selected from CH_2, O S S(O) SO_2, NC_1-C_8alkyl (ncluding linear and branched alkyl groups) NC_1-C_6haloalkyl NC_3-C_8cycloalkyl, $NC(O)C_1$-C_8alkyl (including linear and branched alkyl groups) $NC(O)C_1$-C_6haloalkyl $NC(O)C_3$-C_8cycloalkyl N-benzoyl N-benzyl $NCOOC_1$-C_8alkyl (including linear and branched alkyl groups) $NCOOC_1$-C_6haloalkyl $NCOOC_3$-C_8cycloalkyl, and

Z is selected from hydrogen, hydroxy amino, NC_1-C_8alkyl (including linear and branched alkyl groups) NHC_1-C_6haloalkyl, NHC_3-C_8cycloalkyl $NHC(O)C_1$-C_8alkyl (including linear and branched alkyl groups) $NHC(O)C_1$-C_6haloalkyl $NHC(O)C_3$

C_8cycloalkyl NH-benzoyl NH benzyl NHCOOC -C_8alkyl (including linear and branched alkyl groups), NHCOOC -C_6haloalkyl NHCOOC$_3$-C_8cycloalkyl C_1-C_8alkoxy (ncluding linear and branched alkoxy groups) C_1-C_6haloalkoxy C_3-C_8cycloalkoxy OC(O)C -C_8alkyl (including linear and branched alkyl groups), OC(O)C_1-C_6haloalkyl OC(O)C -C_8cycloalkyl, benzoyloxy benzyloxy OCONHC -C_8alkyl (cluding linear and branched alkyl groups), OCONHC -C_6haloalkyl, OCONHC$_3$-C_8cycloalkyl, C -C_8alkylthio (including linear and branched alkyl groups) C -C_6haloalkylthio, C_3-C_8cycloalkylth o, S(O)C_1-C_8alkyl(including linear and branched alkyl groups) S(O)C_1-C_6haloalkyl S(O)C_3-C_8cycloalkyl, SO_2C_1-C_8alkyl (including linear and branched alkyl groups), SO_2C_1-C_6haloalkyl SO_2C_3-C_8cycloalkyl

In yet other aspects preferred compounds of Form la I (e g I-a or I-b) nd compounds of Formulae II XIX include those compounds m wh ch R_1 or R_1 is selected from



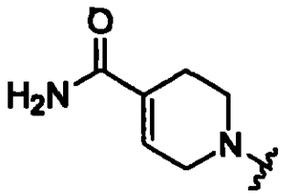


or more preferably a group of formula X

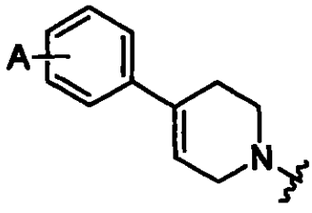
where n X is the po t of attachment to the nitrogen of the imidazo n g

Particularly preferred R_1 groups are shown in the $R_2$2 Matrix and particularly preferred R groups are shown the R 2-Matrix, both in Example 1 which follows

Other preferred R_1 groups include groups of the formula

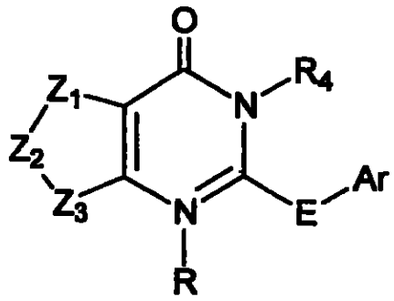


and groups of the formula



where A represents up to three groups independently chosen from hydrogen halogen, alkyl, and alkoxy

Another embodiment of the invention is directed to compounds of Formula XX



Formula XX

or a pharmaceutically acceptable salt thereof, wherein.

E is a single bond, O $S(O)_m$, NR_{10} or $CR_{10}R_{11}$

R_{10} and R_{11} are independently hydrogen or C_1-C_4 alkyl

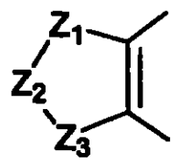
m is 0 1 or 2

Ar is chosen from

phenyl which is mono- d or tri-substituted, 1 naphthyl and 2-naphthyl, each of which is optionally mono- d or tri-substit ted, and optionally mono- d or tri-substituted heteroaryl said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

R is oxygen or absent,

the group



represents a saturated, unsaturated or aromatic 5-membered ring system containing 0 or 1 heteroatoms, wherein

Z_1 is CR_1 CR_1R_1 or NR_1

Z_2 is nitrogen, oxygen, sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen, oxygen sulfur sulfoxide sulfone CR_3, CR_3R_3 or NR_3

R is chosen from halogen hydroxy cyano, amino, optionally substituted alkyl opt onally s bstituted alkenyl opt onally substituted alkynyl optio ally substituted alkoxy optionally substituted mono or dialkylamino optionally substituted (cycloalkyl)alkyl, optionally substituted cycloalkyl optionally substituted heterocycloalkyl, optionally

substituted alkylthio, optionally substituted alkylsulfinyl optionally substituted alkylsulfonyl optionally substituted mono- or d alkylcarboxamide, optionally substituted carbocyclic aryl and opt onally s bst tuted heteroaryl said optionally substituted heteroaryl having from 1 to 3 rings 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

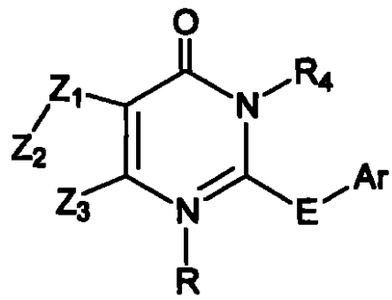
R_1 is chosen from optionally substituted alkyl optionally substituted alkenyl optio ally substituted alkynyl optionally substituted (cycloalkyl)alkyl optionally substituted cycloalkyl opt onally substituted heterocycloalkyl opt onally substituted (heterocycloalkyl)alkyl optionally substituted carbocyclic aryl and optionally substituted heteroaryl said optionally substituted heteroaryl ha ng from 1 to 3 rings, 5 to 7 ring members n each ring and, at least one of sa d rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

R_2 and R_3 are ndependently chosen from hydrogen h loge hydroxy amino, cya o n tro alkyl h loalkyl alkoxy aminoalkyl and mo o and d lkylam no

R_1 R and R_3 are independently chosen from hydrogen halogen alkyl haloalkyl and aminoalkyl

R_2 and R_3 are independently chosen from hydrogen alkyl haloalkyl and aminoalkyl and R_4 s hydrogen alkyl aminoalkyl and haloalkyl

Certain other preferred compounds and pharmaceutically acceptable salts of the invention include those compounds of Formula XX



Formula XX

or a pharmaceut cally acceptable salt thereof wherein

E is a single bond O $S(O)_m$ NR or $CR_{10}R$

R_0 and R_1 are independently hydrogen or C_1-C_4 alkyl

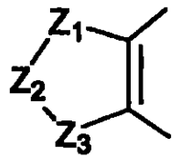
m is 0 1 or 2

R is oxygen or absent,

Ar is chosen from

phenyl which is mono- di- or tri-substituted, 1 naphthyl and 2 naphthyl, each of which is optionally mono- di or tri-substituted and optionally mono- di- or tri-substituted heteroaryl said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

the group



represents a saturated, unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z is CR_1 CR_1R or NR_1

Z_2 is nitrogen, oxygen, sulfur CR_2 CR_2R_2 or NR_2

Z_3 is nitrogen, oxygen, s lfur s lfoxide sulfone CR_3 CR_3R_3 or NR_3

R is chosen from

i) halogen, hydroxy cyano, amino C_1-C_{10}carbhydryl, -O(C_1-C_6carbhydryl) mono or di(C_1 C_6carbhydryl)amino (C_3-C_7cyclocarbhydryl)C -C_4carbhydryl, halo(C C_6)carbhydryl -O(halo(C -C_6)carbhydryl) and S(O)$_n$(C -C_6carbhydryl) -O(C_3 C_7cyclocarbhydryl)C_1-C_4carbhydryl, C_{3-9}heterocycloalkyl (C_{3-9}heterocycloalkyl)C_1 C_4alkyl and S(O)$_n$(C_1-C_6carbhydryl),

where each carbhydryl is independently straight, branched, or cyclic contains zero or 1 or more double or triple bonds,

where each heterocycloalkyl has 1 or 2 ring heteroatoms selected from N O or S and the point of attachment is carbon or nitrogen and

where each carbhydryl, heterocycloalkyl or cyclocarbhydryl is optionally substituted by one or more substituents independently chosen from halogen, hydroxy amino, oxo cyano C_1-C_6alkyl, C_1-C_6alkoxy haloC_1-C_6alkoxy C_1-C_6alkanoyl C_1 C_6alkanoyloxy C_1-C_6alkoxycarbonyl, N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N (C_1 C_6alkanoyloxy)-N-(C_0-C_6alkyl)am no, N-(C -C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, C -C_6alkylsulfonamide C_1-C_6alkylsulfonyl, C_1-C_6alkylsulfonyloxy C -C_6hydroxyalkyl, C_1-C_6alkoxyC -C_6alkyl, C_1-C_6haloalkoxy 5 to 7 membered

heteroaryl 5 to 7 membered heterocycloalkyl mono- and di-(C_1-C_6)alkylamino, N (C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, mono- and d -(C C_6)alkylcarbamoyl XR_C and X Z, and

ii) phenyl which is mono- di or tri-substituted with R_A 1 naphthyl 2 naphthyl pyridyl dihydropyridyl tetrahydropyridyl pyrimidinyl pyrazinyl pyridazinyl thienyl th azolyl oxazolyl isoxazolyl pyrrolyl furanyl and triazolyl each of which is optionally mono- di or tri-substituted with R_A

R is chosen from C -C_{10}alkyl C_2-C_{10}alkenyl C_2-C_{10}alkynyl C_3-C_7cycloalkyl (C_3 C_7cycloalkyl)C -C_4alkyl C_{3-9}heterocycloalkyl (C_{3-9}heterocycloalkyl)C_1-C_4alkyl and halo(C_1-C_6)alkyl each of which is substituted with 0 or more substituents independently chosen from halogen hydroxy amino, oxo, cyano C -C_6alkyl C C_6alkoxy haloC$_1$-C_6alkoxy C_1-C_6alkanoyl C_1-C_6alkanoyloxy C_1-C_6alkoxycarbonyl N-(C -C_6alkanoyl)-N-(C_0-C_6alkyl)amino N-(C -C_6alkanoyloxy)-N-(C_0-C_6alkyl)am no, N-(C -C_6alkoxycarbonyl)-N (C_0-C_4alkyl)am no C C_6alkylsulfo amide C_1-C_6alkylsulfonyl C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C -C_6alkoxyC -C_6alkyl C -C_6h loalkoxy 5 to 7 membered heteroaryl 5 to 7 membered heterocycloalkyl mono- nd d -(C -C_6)alkylamino, N-(C_1-C_6alkanoyl)-N (C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C_1 C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, mono- and di-(C_1-C_6)alkylcarbamoyl, XR_C and X Z,

R_2 and R_3 are independently chosen from hydrogen halogen hydroxy amino, cyano, nitro, C_1-C_6alkyl halo(C_1-C_6)alkyl C_1-C_6alkoxy amino(C -C_6)alkyl and mono and d (C -C_6)alkylamino

R_2 and R_3 are independently chosen from hydrogen halogen C -C_6alkyl halo(C_1-C_6)alkyl and amino(C_1-C_6)alkyl

R_2 and R_3 are independently chosen from hydrogen C_1-C_6alkyl, halo(C_1-C_6)alkyl and am no(C -C_6)alkyl

R_4 is hydrogen C_1-C_6alkyl C_1-C_6aminoalkyl and C_1-C_6haloalkyl

R_A is independently selected at each occurrence from halogen cyano nitro, halo(C -C_6)alkyl h lo(C_1-C_6)alkoxy hydroxy amino C -C_6alkyl substituted with 0-2 R_B, C_2-C_6alkenyl substituted with 0-2 R_B, C_2-C_6alkynyl substituted w th 0 2 R_B, C -C_7cycloalkyl substituted with 0 2 R_B (C -C_7cycloalkyl) C -C_4alkyl substituted with 0-2 R_B, C_1

C_6alkoxy substituted with 0-2 R_B, $NH(C_1$-C_6alkyl) substituted with 0-2 R_B, $N(C_1$ C_6alkyl)(C -C_6alkyl) each C_1-C_6alkyl independently substituted with 0-2 R_B, XR_C, and Y

R_B is independently selected at each occurrence from the gro p consisting of halogen, hydroxy cyano, amino, C_1-C_6alkyl, -$O(C_1$-C_4alkyl), $NH(C_1$-C_4alkyl), $N(C_1$ C_4alkyl)(C_1-C_4alkyl), $S(O)_n$(alkyl) halo(C_1-C_4)alkyl, halo(C -C_4)alkoxy $CO(C_1$ C_4alkyl) $CONH(C_1$-C_4alkyl) $CON(C_1$-C_4alkyl)(C_1-C_4alkyl), XR_C and Y

R_C and R_D, which may be the same or different, are independently selected at each occurrence from

hydrogen, and

straight, branched, or cyclic alkyl groups, including (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, which straight, branched, or cyclic alkyl groups contain zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one o more substituent(s) independently selected from oxo, hydroxy halogen, cyano, amino, C_1-C_6alkoxy $NH(C$ -C_6alkyl) $N(C_1$ C_6alkyl)(C_1-C_6alkyl), -$NHC(=O)(C_1$-C_6alkyl), $N(C_1$-C_6alkyl)$C(=O)(C_1$-C_6alkyl) $NHS(O)_n(C_1$-C_6alkyl), -$S(O)_n(C_1$-C_6alkyl), -$S(O)_nNH(C$ -C_6alkyl) $S(O)_nN(C_1$ C_6alkyl)(C -C_6alkyl) and Z,

X is independently selected at each occurrence from the group consisting of -CH_2- -CHR_D- O- -C(=O)- -C(=O)O- $S(O)_n$ NH NR_D- -C(=O)NH -C(=O)NR_D- -$S(O)_n$NH -$S(O)_nNR_D$- -OC(=S)S- NHC(=O)- $NR_DC(=O)$- $NHS(O)_n$ -$OSiH_2$- -OSiH(C C_4alkyl)- -OSi(C -C_4alkyl)(C_1-C_4alkyl)- and -$NR_DS(O)_n$

Y and Z are independently selected at each occurrence from 3 to 7 membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic which may be further substituted with one or more substituents independently selected from halogen oxo hydroxy amino cyano, C_1-C_4alkyl -$O(C_1$-C_4alkyl) -C(O)(C_1-C_4alkyl) $NH(C_1$-C_4alkyl), $N(C_1$-C_4alkyl)(C_1-C_4alkyl),and $S(O)_n$(alkyl), wherein said 3 to 7 memberered heterocyclic groups contain one or more heteroatom(s) independently selected from N O and S with the point of attachment being either carbon or nitrogen and

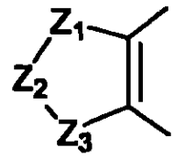
n is independently selected at each occurrence from 0 1 and 2

Preferred compounds and pharmaceutically acceptable salts of Formula XX are those for which

Ar is chosen from

phenyl which is mono- di or tri-substituted with R_A and 1 naphthyl 2-naphthyl, pyridyl pyrimidinyl pyrazinyl, pyridizinyl thienyl thiazolyl oxazolyl, isoxazolyl pyrrolyl furanyl and triazolyl each of which is optionally mono- di or tri-substituted with R_A

the group



represents a saturated unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z_1 is CR CR R_1 or NR_1

Z_2 is nitrogen, oxygen, sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen oxygen, sulfur sulfoxide sulfone, CR_3, CR_3R_3 or NR_3

R_1 is chosen from

i) halogen hydroxy cyano amino C_1-C_{10}carbhydryl -O(C -C_6 carbhydryl) mono o di (C C_6carbhydryl)amino, (C_3-C_7cycloalkyl)-C_1-C_4carbhydryl halo($C_1$$C_6$)carbhydryl O(halo(C C_6)carbhydryl) and S(O)$_n$(C -C_6carbhydryl), -O(C_3-C_7cycloalkyl)C C_4carbhydryl and S(O)$_n$(C C carbhydryl),

where each carbhydryl is independently straight, branched or cyclic, contains zero or 1 or more double or triple bonds, and is optionally substituted with one or more substituents independently chosen from halogen hydroxy amino, oxo cyano, C_1 C_1-C_4alkoxy and mono- or di(C_1-C_4)alkylamino

and

where each C -C_7cycloalkyl is optionally substituted by one or more substituents independently chose from halogen amino hydroxy oxo, cyano, C -C_4alkoxy and mono- o di(C C_4)alkylamino,

and

i) phenyl which is mono- di or tri-substituted with R 1 naphthyl 2 naphthyl pyridyl dihydropyridyl, tetrahydropyridyl pyrimidinyl pyrazinyl, pyridizinyl thienyl

thiazolyl, oxazolyl isoxazolyl pyrrolyl furanyl, and triazolyl each of which is optionally mono- di or tri-substituted with R_A,

R_1 is chosen from

C_1-C_{10}carbhydryl, (C_3-C_7cycloalkyl)C_1-C_4carbhydryl, halo(C_1-C_6)carbhydryl

where each carbhydryl is independently straight, branched, or cyclic contains zero or 1 or more double or triple bonds, and is optionally substituted with one or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano C_1-C_4alkoxy and mono- or di(C_1-C_4)alkylamino,

and

where each C_3-C_7cycloalkyl is optionally substituted by one or more substituents independently chosen from halogen amino, hydroxy oxo cyano C_1-C_4alkoxy and mono- or di(C_1-C_4)alkylamino

and

ii) phenyl which is mono- di or tri-substituted with R_A, 1 naphthyl 2-naphthyl pyridyl, dihydropyridyl tetrahydropyridyl pyrimidinyl, pyrazinyl pyridizinyl, thienyl, thiazolyl oxazolyl, isoxazolyl, pyrrolyl furanyl and triazolyl each of which is optionally mono- di- or tri-substituted with R_A

R_2 and R_3 are dependently chosen from hydrogen halogen, hydroxy amino, cyano nitro, C_1-C_6alkyl, halo(C_1-C_6)alkyl C_1-C_6alkoxy amino(C_1-C_6)alkyl, and mono and di(C_1-C_6)alkylamino

R_2 and R_3 are independently chosen from hydrogen, halogen C_1-C_6alkyl halo(C_1-C_6)alkyl, and amino(C_1-C_6)alkyl

R_2 and R_3 are independently chosen from hydrogen C_1-C_6alkyl halo(C_1-C_6)alkyl, and amino(C_1-C_6)alkyl

R_4 is hydrogen or C_1-C_6alkyl

R_A is independently selected at each occurrence from halogen, cyano nitro halo(C_1-C_6)alkyl halo(C_1-C_6)alkoxy hydroxy amino, C_1-C_6alkyl substituted with 0-2 R_B, C_2-C_6alkenyl substituted with 0-2 R_B, C_2-C_6alkynyl substituted with 0- R_B C_3-C_7cycloalkyl substituted with 0-2 R_B, (C_3-C_7cycloalkyl) C_1-C_4alkyl substituted with 0-2 R_B C_1-C_6alkoxy substituted with 0-2 R_B, NH(C_1-C_6alkyl) substituted with 0 2 R_B, N(C_1-C_6alkyl)(C_1-C_6alkyl) each C_1-C_6alkyl independently substituted with 0-2 R_B XR_C and Y

R_B is ndependently selected at each occurrence from the group consisting of halogen hydroxy cyano amino C C_4alkyl -O(C_1-C_4alkyl) NH(C -C_4alkyl) N(C_1 C_4alkyl)(C_1-C_4alkyl), S(O)$_n$(alkyl) halo(C_1-C_4)alkyl halo(C_1-C_4)alkoxy CO(C_1 C_4alkyl), CONH(C -C_4alkyl), CON(C_1-C_4alkyl)(C -C_4alkyl) XR_C and Y

R_C and R_D, which may be the same or different, are ndependently selected at each occurrence from

hydrogen nd

straight, branched, or cycl c alkyl groups, including (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, which straight, branched or cyclic alkyl groups contain zero or one or more double or triple bonds each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy halogen cyano amino, C -C_6alkoxy NH(C -C_6alkyl), N(C_1 C_6alkyl)(C_1-C_6alkyl), NHC(=O)(C_1-C_6alkyl), N(C -C_6alkyl)C(=O)(C_1-C_6alkyl) NHS(O)$_n$(C_1-C_6alkyl), S(O)$_n$(C_1-C_6alkyl), -S(O)$_n$NH(C_1-C_6alkyl), S(O)$_n$N(C_1 C_6alkyl)(C -C_6alkyl), and Z,

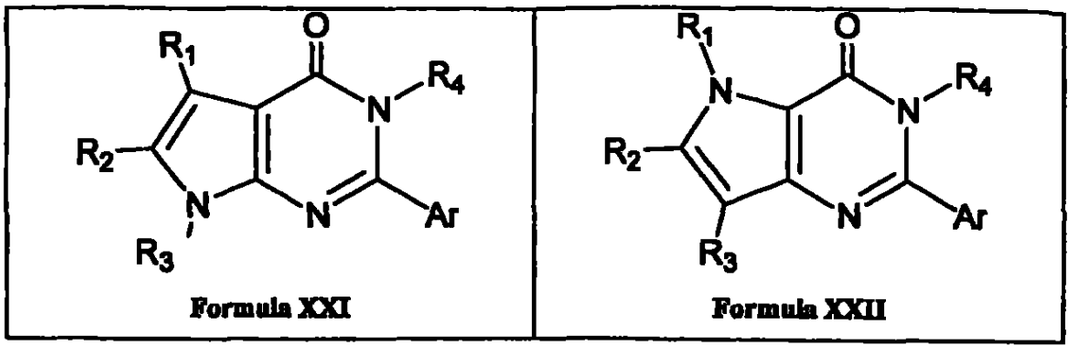
X dependently selected at each occurrence from the group cons sting of -CH -CHR_D- O -C(=O)- -C(=O)O- -S(O)$_n$- NH NR_D- -C(=O)NH -C(=O)NR_D- -S(O) NH -S(O)$_n$$NR_D$- -OC(=S)S NHC(=O)- NR_DC(=O) NHS(O)$_n$ -OSiH_2 -OS H(C_1 C_4alkyl)- -OSi(C -C_4alkyl)(C_1-C_4alkyl)- and –NR_DS(O)$_n$

Y and Z are ndependently selected at each occurrence from 3 to 7 membered carbocyclic or heterocyclic groups which are saturated unsaturated or aromatic, wh ch may be further subst tuted with one or more substituents ndependently selected from halogen oxo hydroxy amino, cyano C_1-C_4alkyl -O(C_1-C_4alkyl), NH(C -C_4alkyl) N(C -C_4alkyl)(C_1-C_4alkyl),and -S(O)$_n$(alkyl),

wherein said 3 to 7 memberered heterocyclic groups contain one or more heteroatom(s) ndependently selected from N O and S w th the point of attachm nt being either carbon or nitrogen and

n is ndependently selected at each occurrence from 0 1 and 2 Such compounds will be referred to as compounds of Form la XXA

The invention is particularly directed to compounds and salts of the following Formula



Formula XXI Formula XXII

Preferred compounds and salts of Formula XXI and Formula XXII

R_1 or R_1 are as defined for Formula XX, or preferably as defined for Form la XXA.

R_2 is selected from hydrogen, methyl, and ethyl

R_3 is selected from hydrogen and C_1-C_6alkyl and

Ar is selected from the group consisting of phenyl pyridyl which is mono- di or tris bstituted with substituents independently chosen from halogen, cyano nitro, halo(C_1-C_6)alkyl

halo(C_1-C_6)alkoxy hydroxy amino, C_1-C_6alkyl C_2-C_6alkenyl C_2-C_6alkynyl C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C_1-C_4alkyl C_1-C_6alkoxy mono- and di(C_1 C_6alkyl)amino amino(C -C_6)alkyl and mono- and di(C_1-C_6alkyl)amino, wherein, in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula XXI or XXII is substituted

Compounds of the invention are useful in treating a variety of conditions including affective disorders, anxiety disorders, stress disorders, eating disorders, and drug addiction

Affective disorders include all types of depression, bipolar disorder cyclothymia, and dysthymia.

Anxiety disorders include generalized anxiety disorder panic phobias and obsessive-compulsive disorder

Stress-related disorders include post-traumatic stress disorder hemorrhagic stress, stress-induced psychotic episodes, psychosocial dwarfism stress headaches, stress-induced immune systems disorders such as stress-induced fever and stress-related sleep disorders

Eating disorders include anorexia nervosa, bulimia nervosa, and obesity

Modulators of the CRF receptors are also useful in the treatment (e g. symptomatic treatment)of a variety of neurological disorders including supranuclear palsy AIDS related

dementias, multiinfarct dementia, neurodegenerative disorders such as Alzheimer s disease, Parkinson s disease, a d Hunti gton s disease head trauma, spinal cord trauma schemi neuronal damage, amyotroph lateral sclerosis, disorders of pain perception such as fibromyalgia and epilepsy

Additionally compounds of Formula I are useful as modulators of the CRF receptor in the treatment (e g., symptomatic treatment) of a number of gastrointestinal card ovascular hormonal utoimmune and inflammatory conditions Such conditions include irritable bowel syndrome, ulcers Crohn s disease spastic colon, diarrhea, post operative ilius and colonic hypersensiti ity associated with psychopathological disturbances or stress, hypertension, tachycardia, congesti e heart failure infertility euthyroid sick syndrome, inflammatory conditions effected by rheumatoid arthritis and osteoarthritis, pain asthma, psoriasis and allerg es

Compounds of Formula I are also useful as modulators of the CRF1 receptor in the treatment of an mal disorders associated with aberrant CRF levels These conditions include porcine stress syndrom bo ne sh pp g fever eq ine paroxysm l fibrillation, and dysfunct ons nduced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs, psychosocial dwarfism and hypoglycemia.

Typical subjects to wh h compounds of the nvention may be adm istered w ll be mammals, particularly primates, especially h mans Fo veterinary appl cations, a wide variety of subjects will be suitable e g livestock such as cattle, sheep goats cows, swine and the like poultry such as chickens, ducks, geese turkeys, and the like and othe domesticated animals particularly pets such as dogs and cats For diagnostic or research applications, a wide variety of mammals will be suitable subjects including rodents (e g mice, rats, hamsters), rabbits, primates, and swine such as inbred pigs and the like Additionally for *n vitro* applications, such as *i tro* d agnostic and research applicat ons, body flu ds (e g blood plasma, serum CSF lymph cellular interstitial fluid aqueous humor saliva, synovial fluid, feces, or urine) and cell and tissue samples of the above subjects will be suitable for use

The CRF binding compounds provided by this nvention and labeled derivatives thereof are also useful as standards and reagents n determining the ability of test compounds (e g a potential pharmaceutical) to bind to a CRF receptor

Labeled derivatives the CRF antagonist compounds provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

More particularly compounds of the invention may be used for demonstrating the presence of CRF receptors in cell or tissue samples This may be done by preparing a plurality of matched cell or tissue samples, at least one of which is prepared as an experiment sample and at least one of which is prepared as a control sample The experimental sample is prepared by contacting (under conditions that permit binding of CRF to CRF receptors within cell and tissue samples) at least one of the matched cell or tissue samples that has not previously been contacted with any compound or salt of the invention with an experimental solution comprising the detectably-labeled preparation of the selected compound or salt at a first measured molar concentration The control sample is prepared by n the same manner as the experimental sample and is incubated in a solution that contains the same ingredients as the experimental solution but that also contains an unlabelled preparation of the same compound or salt of the invention at molar concentration that is greater than the first measured molar concentration

Th experimental and control samples are then washed to remove unbound detectably labeled compound The amount of detectably labeled compound remaining bound to each sample is then measured and the amount of detectably labeled compound in the experimental and control samples is compared A comparison that indicates the detection of a greater amount of detectable label in the at least one washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of CRF receptors in that experimental sample

The detectably-labeled compo nd used in this procedure may be labeled with any detectable label, such as a radioactive label, a b ological tag such as biotin (which can be detected by b nding to detectably labeled avidin) an enzyme (e g alkaline phosphatase, beta galactosidase or a like enzyme that can be detected ts activity in a colorimetric assay) or a directly or indirectly luminescent label When tissue sections are used in this procedure and the detectably labeled compound is radiolabeled, the bound labeled compound may be detected autoradiographically to generate an autoradiogram When autoradiography is used, the amount of detectable label in an experimental or control sample may be measured by viewing the autorad ograms and comparing the exposure density of the autoradiograms.

The present invent on lso perta ns to m thods of inhibiti g th bi ding of CRF to CRF receptors (preferably CFR1 receptors) whi h methods involve contacti g a solut on containing a CRF antagonist compound of the invention with cells expressing CRF receptors, where n the compou d is present in th solution at a concentration sufficient to inhibit CRF binding to CRF receptors *in tro* This method in ludes hibit g the binding of CRF to CRF receptors *i vivo* e g in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of CRF to CRF receptors *n itro* In one embodiment, such methods are useful in treating physiological disorders associated with excess concentrations of CRF The amount of a compound that would be sufficient to inhibit the binding of a CRF to the CRF receptor may be readily determined ia a CRF receptor bindi g assay (see, e g Example 51), or from the EC_{50} of a CRF receptor functional assay such as a standard assay of CRF receptor med ated chemotaxis The CRF receptors used to determine *in vitro* binding may be obtained from a variety of sources, fo example from cells that naturally express CRF receptors, e g IMR32 cells or from cells expres ng clo ed h man CRF receptors

The present ent on also pertains to methods fo altering th act ty of CRF receptors, sa d method comprising expos g cells expressing such receptors to an effective amount of a compound of the nvention wherein the compound is present i the solution at a concentration sufficient to specifically alter the signal transduction activity in response to CRF in cells expressing CRF receptors *n tro* preferred cells for this purpose are those that express high levels of CRF receptors (i e equal to or greater than the number of CRF1 receptors per cell fo nd in d fferentiated IMR 32 human neuroblastoma cells) with IMR 32 cells bei g particularly preferred for testing the concentration of a compound required to alter the activity of CRF1 receptors This method includes altering the signal transduction activity of CRF receptors *i vo* e g n a pat ent given an amount of a compound of Form la I that would be sufficient to alter the s gnal transduction acti ity in response to CRF in cells expres g CRF receptors *m tro* The am nt of compound that would be fficient to alter the signal transduction activity in response to CRF of CRF receptors may also be determined via an assay of CRF receptor mediated signal transduction such as an assay wherein the binding of CRF to a cell surface CRF receptor effects a changes in reporter gene expression

The present in ention also perta ns to packaged pharmac utical compos tions for treating disorders responsive to CRF receptor modulation e g eating disorders, depression

or stress. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one CRF1 receptor modulator as described supra and instructions for using the treating disorder responsive to CRF1 receptor modulation in the patient.

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Chemical description nd terminology

The compounds herein described may have one or more asymmetric centers or planes Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racem c forms. It is well known in the art how to prepare
10 optically active forms, such as by resolution of racemic forms (racemates) by asymmetric synthesis, or by synthesis from optically active starting materials Resolution of the racemates can be accomplished, for exampl by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the
15 compounds described herein, and all such stable isomers are contemplated in the present invention *Cis* and *trans* geometric somers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms All chiral (enantiomeric and diastereomeric), and racemic forms, as well as all geometric isome ic forms of a structure are intended unless the specific stereochemistry or isomeric
20 form is specifically indicated

When any variable occurs more than one time in any const tuent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence Thus, for example, if a group is shown to be substituted with 0-2 R then said group may optionally be substituted with up to two R groups and R at each occurrence is
25 selected independently from the definition of R Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Formula I includes, but is not limited to compounds of Formula I, IA, and II XXII As indicated above, various substituents of the various formulae (compounds of Formula I I IA, and II XXII) are optionally substituted including Ar^1 Ar^2 R R^2 and R^3 of Formula I
30 and subformulae thereof, and such s bstituents as recited in the s b formulae such as Formula I and subformulae The term substituted, as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group of substituents, provided that the designated atom s normal valence is not

exceeded and that the substitut on results in a stable compound When a substituent is oxo (keto e =O) then 2 hydrogens on an atom are replaced The present inventio is intended to include all isotopes (including radio sotopes) of atoms occurring n the present compounds

When substituents such as Ar R R_2, R_3, R_4 and R_5 are further substituted, th y may be so substituted at one or more available positions, typically 1 to 3 or 4 positions, by one or more suitable groups such as those disclosed herein Suitable groups that may be present on a substituted Ar R R_2, R_3, R_4 and R_5 or other group include g halogen cyano hydroxyl nitro azido alkanoyl (such as a C_1-C_6 alkanoyl group s ch as acyl or the like) carboxamido alkyl groups (including cycloalkyl groups having 1 to about 8 carbon atoms, preferably 1 2, 3 4 5 or 6 carbon atoms) alkenyl and alkynyl groups (including groups having one or more unsaturated linkages and from 2 to about 8 preferably 2, 3 4 5 or 6 carbon atoms) alkoxy groups hav ng one or more oxygen linkages and from 1 to about 8 preferably 1 2 3 4 5 or 6 carbon atoms aryloxy such as phenoxy lkylthio groups i cluding those having one or more thioether linkages and from 1 to about 8 carbon atoms, preferably 1 2 3 4 5 or 6 carbon atoms alkylsulfinyl groups cludi g those h vi g one or more sulfinyl linkages and from 1 to about 8 carbon atoms, preferably 1 2, 3 4 5 or 6 carbon atoms, alkylsulfonyl groups including those ha ing one or more s lfonyl linkages and from 1 to about 8 carbon atoms, preferably 1 2, 3 4 5 or 6 carbon atoms· aminoalkyl groups including groups ha ing one or more N atoms and from 1 to about 8 preferably 1 2, 3 4 5 or 6 carbon atoms carbocyclic aryl ha ing 6 or more carbons and one or more rings, (*e g.* phenyl b phenyl naphthyl or the like, each ring erthe substituted or unsubstituted aromatic) arylalkyl ha i g 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with benzyl be g a preferred aryl lkyl group arylalkoxy ha ing 1 to 3 separate or fused rings and from 6 to about 18 ring carbon atoms, with O-benzyl being a preferred arylalkoxy group or a saturated unsaturated or aromatic heterocyclic group ha ing 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N O or S atoms, g coumarinyl quinolinyl isoquinolinyl quinazolinyl pyridyl pyrazinyl pyrimidyl furanyl pyrrolyl thienyl thiazolyl triaz nyl oxazolyl isoxazolyl imidazolyl indolyl benzofuranyl benzothiazolyl tetrahydrofuranyl tetrahydropyranyl piperidinyl morph linyl piperazinyl and pyrrolidinyl Such heterocyclic groups may be further substituted *e g* with hydroxy alkyl alkoxy halogen and amino

As used here n alkyl is intended to incl de both branched and straight-chain saturated aliphatic hydrocarbon groups, having the specified number of carbon atoms

Examples of alkyl include but are not limited to, methyl, ethyl *n*-propyl, -propyl *n*-butyl *s*-butyl *t*-butyl, *n*-pentyl and *s*-pentyl Preferred alkyl gro ps are C -C_{10} alkyl groups Especially preferred alkyl groups are methyl, ethyl propyl butyl, and 3 pentyl The term C_1 $_4$ alkyl as used herein includes alkyl groups consisting of 1 to 4 carbon atoms, which may contain a cyclopropyl moiety Suitable examples are methyl ethyl, and cyclopropylmethyl

The term carbhydryl refers to both branched and straight-chain hydrocarbon groups, which are saturated or unsaturated. In other words, a carbhydryl group may be alkyl alkenyl or alkynyl The number of carbon atoms may be specified as indicated abov

Cycloalkyl is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl Cycloalkyl groups typically will have 3 to about 8 ring members.

In the term (C_3-C_7cycloalkyl)C_1-C_4alkyl cycloalkyl and alkyl are as defined abo e, and the po t of attachment is on the alkyl group This term encompasses, but is not limited to, cyclopropylmethyl cyclohexylmethyl and cyclohexylmethyl

Alkenyl is intended to include hydrocarbon chains of e ther a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds, which may occur in any stable point along the chain such as ethenyl and propenyl Alkenyl groups typically will have 2 to about 8 carbon atoms, more typically 2 to about 6 carbon atoms

Alkynyl is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more carbon-carbon triple bonds, which may occur in any stable point along the chain, such as ethynyl and propynyl Alkynyl groups typically will have 2 to about 8 carbon atoms, more typically 2 to about 6 carbon atoms

carbhydryl s independently straight, branched, o yclic conta ns zero or 1 or more double or triple bonds

Haloalkyl is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms substituted w th 1 or more halogen atoms Examples of haloalkyl include but are not limited to, mono- d or tri fluoromethyl mono- di or tri-chloromethyl, mono- di tri tetra or penta fluoroethyl, and mono- di tri tetra or penta-chloroethyl Typical haloalkyl groups will have 1 to about 8 carbon atoms, more typically 1 to about 6 carbon atoms

Alkoxy represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge Examples of alkoxy include, but are not limited to, methoxy ethoxy *n*-propoxy *i*-propoxy n-butoxy 2-butoxy *t* butoxy *n*-pentoxy

2-pentoxy 3-pentoxy isopentoxy neopentoxy *n*-hexoxy 2-hexoxy 3 hexoxy and 3 methylpentoxy Alkoxy groups typically have 1 to about 8 carbon atoms, more typically 1 to about 6 carbon atoms

"Haloalkoxy represents haloalkyl group as defined above with the indicated number of carbo atoms attached through an oxygen bridge

As used herein, the term alkylthio includes those groups having one or more thioether linkages and preferably from 1 to about 8 carbon atoms, more typically 1 to about 6 carbon atoms

As used herein, the term "alkylsulfinyl includes those groups ha ing one or more sulfoxide (SO) linkage groups and typically from 1 to about 8 carbon atoms, more typ cally 1 to about 6 carbon atoms

As used herein the term alkylsulfonyl ncludes thos groups having one or more sulfonyl (SO_2) linkage groups and typically from 1 to about 8 carbon atoms, more typically 1 to about 6 carbon atoms

As sed herei the term 'alkyl m no ncludes those gro ps hav g one or more primary secondary and/or tertiary amine groups a d typically from 1 to abo t 8 carbon atoms, more typically 1 to bout 6 carbon atoms

Halo or "halogen as used herein refers to fluoro hloro bromo, or iodo and counter-ion is used to represent a small negatively charged spec es such as chloride bromide, hydrox de acetate, sulfate, nd the like

As used herem carbocyclic group s intended to mean any stable 3 to 7 membered monocycl c or bicyclic or 7-to 13-membered bicyclic or tr cyclic group, any of which may be saturated partially unsaturated, or aromatic In addition to those exemplified elsewhere herein, examples of such carbocycles include, but are not l mited to cyclopropyl cyclobutyl cyclopentyl cyclohexyl, cycloheptyl adamantyl cyclooctyl, [3.3 0]bicyclooctanyl [4 3 0]bicyclononanyl [4 4 0]bicyclodecanyl [2.2 2]b ycloоctanyl fluorenyl phe yl naphthyl indanyl and tetrahydronaphthyl

As used herein the term "heterocyclic group is intended to include saturated, partially unsaturated o unsaturated (aromatic) groups ha ing 1 to 3 (preferably fused) rings with 3 to about 8 members per ring at least one ring containing an atom selected from N O or S The nitrogen and sulfur heteroatoms may optionally be oxidized The term or heterocycloalkyl is sed to refer to saturated heterocycl groups ha ng one o more non carbon ring atoms (e g N O S P Si or the like) and a specified number of carbon atoms

Thus, a C_{3-9}heterocycloalkyl is a cyclic group having between 3 and 9 ring carbon atoms and at least one ring heteroatom

The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable A nitrogen in the heterocycle may optionally be quaternized. As used herein, the term aromatic heterocyclic system is intended to include any stable 5-to 7 membered monocyclic or 10- to 14-membered bicyclic heterocyclic aromatic ring system which comprises carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N O and S It is preferred that the total number of S and O atoms in the aromatic heterocycl is not more than 2, more preferably not more than 1

Examples of heterocycles include, but are not limited to those exemplified elsewhere herein and further include acridinyl, azocinyl, benzimidazolyl, benzofuranyl benzothiofuranyl, benzothiophenyl benzoxazolyl benzthiazolyl benztriazolyl benztetrazolyl, benzisoxazolyl benzisothiazolyl benzimidazolinyl, carbazolyl NH-carbazolyl carbolinyl chromanyl chromenyl cinnolinyl decahydroquinolinyl 2*H*,6*H* 1 5,2-dithiazinyl, dihydrofuro[2 3-*b*]tetrahydrofuran, furanyl furazanyl imidazolidinyl, imidazolinyl imidazolyl, 1H indazolyl indolenyl indolinyl, indolizinyl, indolyl 3*H* indolyl isobenzofuranyl isochromanyl isoindazolyl isoindolinyl isoindolyl, isoquinolinyl isothiazolyl isoxazolyl, morpholinyl naphthyridinyl octahydroisoquinolinyl oxadiazolyl, 1,2 3-oxadiazolyl, 1 2 4-oxad azolyl 1 2 5oxadiazolyl 1,3 4-oxadiazolyl oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl phenanthridinyl, phenanthrolinyl phenazinyl phenothiazinyl phenoxathiinyl, phenoxazinyl phthalazinyl, piperazinyl, piperidinyl pteridinyl purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl pyridazinyl pyridooxazole, pyridoimidazole pyridothiazole pyridinyl pyridyl, pyrimidinyl pyrrolidinyl, pyrrolinyl 2*H* pyrrolyl pyrrolyl quinazolinyl quinolinyl 4H-quinolizinyl, quinoxalinyl quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl tetrahydroquinolinyl, 6*H* 1,2 5 thiadiazinyl, 1,2 3-thiadiazolyl 1,2,4-thiadiazolyl 1,2,5 thiadiazolyl 1 3 4-thiadiazolyl thianthrenyl thiazolyl, thienyl, thienothiazolyl thienooxazolyl, thienoimidazolyl thiophenyl, triazinyl, 1,2 3 triazolyl, 1,2 4-triazolyl 1,2 5-triazolyl 1,3 4-triazolyl and xanthenyl

Preferred heterocyclic groups include but are not limited to pyridinyl, py imidinyl, furanyl thienyl pyrrolyl, pyrazolyl pyrrolidinyl morpholinyl piperidinyl, piperazinyl and

imidazolyl Also included are fused ring and spiro compo ds containing, for example, the above heterocycles

As used herein the term carbocyclic ryl" includes groups that contain 1 to 3 separate or fused rings and from 6 to about 18 ring atoms, without hetero atoms as ring members. Specifically preferred carbocyclic aryl groups include phenyl and naphthyl nclud ng 1 napthyl and 2 naphthyl

As used herein pharmaceutically cceptable salts refer to deri atives of the disclosed compounds wherein the parent compound s mod fied by mak ng on toxic acid or base salts thereof, and further refers to pharmaceutically acceptable solvates of such compounds and such salts Examples of pharmaceutically acceptable salts include, but are not limited to m eral or organic acid salts of basic residues such as amines alkali or organic salts of acidic residues such as carboxylic ac ds and the like The pharmaceutically acceptable salts include the conventional non tox c salts and the quaternary ammonium salts of the parent compound formed for example, from non-toxic inorganic or organic acids For example, conventional non tox ac d salts l de those d ved from norgan ac ds such as hydrochloric, hydrobromic, sulfuric sulfamic phosphoric, n tric and the like and the salts prepared from organ c ac ds such as acetic propionic, succin c, glycolic stearic lact c malic, tartaric citric, ascorb c, pamo c, m lefic hydroxym le c, phenylacetic, glutam c, benzoic sal cylic, mesylic sulfanilic, 2 acetoxybenzoic, fumaric, tolue esulfonic, metha esulfonic, ethane disulfonic oxal c, isethionic HOOC-$(CH_2)_n$-COOH where n is 0-4 and the like The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound that contains a basic or acidic moiety by conventio al chemical methods Generally such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like) o by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid Such reactions are typically carried out i wate or in an organic solvent, or in a mixture of the two Generally non-aqueous media like ether ethyl acetate, ethanol isopropanol or acetonitrile are preferred where practicable Lists of additional su table salts may be found e g in *R ington Pharmaceutical Sciences* 17th ed Mack Publishing Company Easton PA p 1418 (1985)

"Prodrugs are intended to include any compounds that become compounds of Formula I when admin stered to a mammalian subject, e.g upon metabolic process ng of the prodrug Examples of prodrugs include, but are not l mited to, acetate, formate and benzoate

and like derivatives of functional groups (such as alcohol or amine groups) in the compounds of Formula I

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture and subsequent formulation into an effective therapeutic agent. The term therapeutically effective amount" of a compound of this invention means an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as an amelioration of symptoms e g an amount effective to antagonize the effects of pathogenic levels of CRF or to treat the symptoms of stress disorders, affective disorder anxiety or depression

Pharmaceutical Preparations

The compounds of general Formula I may be administered orally topically transdermally parenterally by inhalation or spray or rectally or vaginally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adj ants and vehicles Th term parenteral as used here n ncludes s bcutaneous intravenous, ntramusc lar intrathecal and like types of injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier One o more compounds of general Formula I may be present in association with one or more non toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use for example as tablets troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion hard or soft capsules, or syrups or elixirs

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents coloring agents and preserving agents in order to provide pharmaceutically legant and palatable preparations Tablets contain the active ingredient in admixture with non toxic pharmaceutically acceptable excipients that are s itable for the manufacture of tablets These excipients may be for example, inert diluents, such as calcium carbonate

sodium carbonate, lactose, calci m phosphate or sodium phosphate granulating and d sintegrat ng agents, for example corn starch, or lgi ic acid binding agents, for example starch gelatin or acacia, and lubricating agents, for example magnes um stearate, stearic acid or talc The tablets may be ncoated or they may be coated by known techniques to delay disintegration and absorption in the gastromtestin l tract and thereby provide a sustained action over a longer period For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calci m phosphate or kaolin or as soft gelatin capsules wherein the actrve ingredient is mixed with water or an oil medium for example peanut oil liquid paraffin or ol ve oil

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions· Such exc pients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose hydropropylmethylcell lose sod m alg ate polyv ylpyrrol done, gum tragacanth d gum acac a d spers g or wetting agents may be a naturally-occurring phosphatide for example lecithin, or condensation prod cts of n alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chai aliphatic alcohols, for example heptadecaethyleneoxycetanol or condensation products of ethylene oxide with partial esters derived from fatty ac ds and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation prod cts of ethylene oxide with partial esters derived from fatty acids and hex tol anhydrides, for example polyethylene sorbitan monooleate The aqueous suspensions may also contain one or more preservatives, for example ethyl or n propyl p-hydroxybenzoate one or more coloring agents, one or more flavoring agents, and one or more sweetening agents such as sucrose or saccharin

Oily suspensions may be formulated by suspend ng the acti e ingred ents n a vegetable oil for example arachis oil olive oil sesame oil or coconut oil or m a m neral o l such as liquid paraffin The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations These compositions may be preserved by the addit on of an anti-oxidant such as ascorbic acid

Dispersible powders and granules su table for preparation of an aqueous suspension by the addition of water pro ide the actrve ingred ent in admixture with a dispersing or

wetting agent, suspending agent and one or more preservatives Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil in water emulsions The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil for example liquid paraffin or mixtures of these Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide for example polyoxyethylene sorbitan monoleate The em lsions may also contain sweetening and flavoring agents

Syrups and elixirs may be formulated with sweetening agents, for example glycerol propylene glycol, sorbitol or sucrose Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents The pharmaceutical compos tions may be in the form of a sterile injectable aqueous or oleaginous suspension This suspens on may be formulated accord ng to the known art using those suitable d spers ng or wetting agents and suspending agents that have been mentioned above The sterile injectable preparation may also be sterile injectable solution or suspension in non-toxic parentally acceptable dilutent or solvent, for example as a solution in 1,3-butaned ol Among the acceptable vehicles and sol ents that may be mployed are water Ringer's sol tion and isotonic sodium chloride solution In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides In addition fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may lso be administered in the form of suppositories, e g for rectal administration of the drug. These compos tions can be prepared by mixing the drug with a suitable non irritating excipient that is solid at ordinary temperatures but liquid at body temperature and will therefore melt in the body to release the drug Such materials include cocoa butter and polyethylene glycols

Compounds of general Formula I may be administered parenterally in a sterile medi m The drug, depending on the vehicle and concentration used can either be

suspended or dissolved n the vehicle Advantageously one or more adjuvants such as preservat ves, buffering agents, or local nesthetics can lso be present i the vehicle

Dosage levels of the order of from about 0 05 mg to about 100 mg per kilogram of body weight per day are useful in the treatment of the above-mdicated condrtions, preferred dosages range from about 0 1 to about 30 mg per kg and more preferably from about 0 5 to about 5 mg per kg per subject per day The amount of actrve ingredient that may be combined with fhe carrie materials to produce a single dosage form will ary depending upon the host treated and the particular mode of administration Dosage unit forms will generally contain between from about 0 1 mg to about 750 mg of an act ve ingredient

Frequency of dosage may also vary depending on the compound used and the particular disease treated However for treatment of most CNS and gastrointestinal disorders, dosage regimen of four t mes daily preferably three times daily more preferably two t mes daily and most preferably once da ly is contemplated For the treatment of stress and depression a dosage regimen of 1 or 2 times daily is particularly preferred

It w ll be nderstood however that the spec f dose le el fo any particula patient will depend upon a ariety of factors including th acti ity of the specif c compound employed the age, body weight, general health sex diet, time of admin stration route of adm nistration, and rate of excretion drug combinat on (i.e othe drugs being used to treat the patient) and the seventy of the particular d sease undergoing therapy

Preferred compounds of the invention will ha e certain pharmacological properties Such properties include, but are not l mited to oral bioavailability such that the preferred oral dosage forms discussed above can provide therapeutically effectrve levels of the compound *in vivo* Penetration of the blood brain barrier is necessary for most compo nds used to treat CNS disorders, while low brain levels of compounds used to treat perıphereal disorders are generally preferred

Assays may be used to predict these desirable pharmacological properties Assays used to predict bioavailability include transport across human i testinal cell monolayers, including Caco-2 cell monolayers Toxicity to cultured hepatocyctes may be used to predict compound toxicity with non toxic compou ds be g preferred Penetrat o f the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals g ven the compound e g intra enously

Percentage of serum protein binding may be predicted from albumin b nding assays Examples of such assays are described in a review by Oravcová, et al (Journal of

Chromatography B (1996) volume 677 pages 1 27) Preferred compounds exhibit reversible serum protein binding Preferably this binding is less than 99%, more preferably less than 95%, even more preferably less than 90%, and most preferably less than 80%

Frequency of administration is generally inversely proportional to the *in vivo* half life of a compound *I vivo* half lives of compounds may be predicted from *in vitro* assays of microsomal half life as described by Kuhnz and Gieschen (Drug Metabolism and Dispos tion (1998) volume 26 pages 1120-1127) Preferred half lives are those allowing for a preferred frequency of administration

As discussed above, preferred compounds of the invention exhibit good activity in standard *in vitro* CRF receptor binding assays, preferably the assay as specified in Example 51 which follows References herein to standard *in tro* receptor binding assay" are tended to refe to standard assay protocols such as that protocol defined in Example 51 which follows Generally preferred compounds of the invention have an IC_{50} (half-maximal hib tory concentration) of about 1 micromolar or less, still more preferably and IC_{50} of about 100 nanomolar or less even more preferably an IC_{50} of about 10 nanomolar or less or e 1 nanomolar or less in such a defined standard *in tro* CRF receptor binding assay as exemplified by Example 51 which follows.

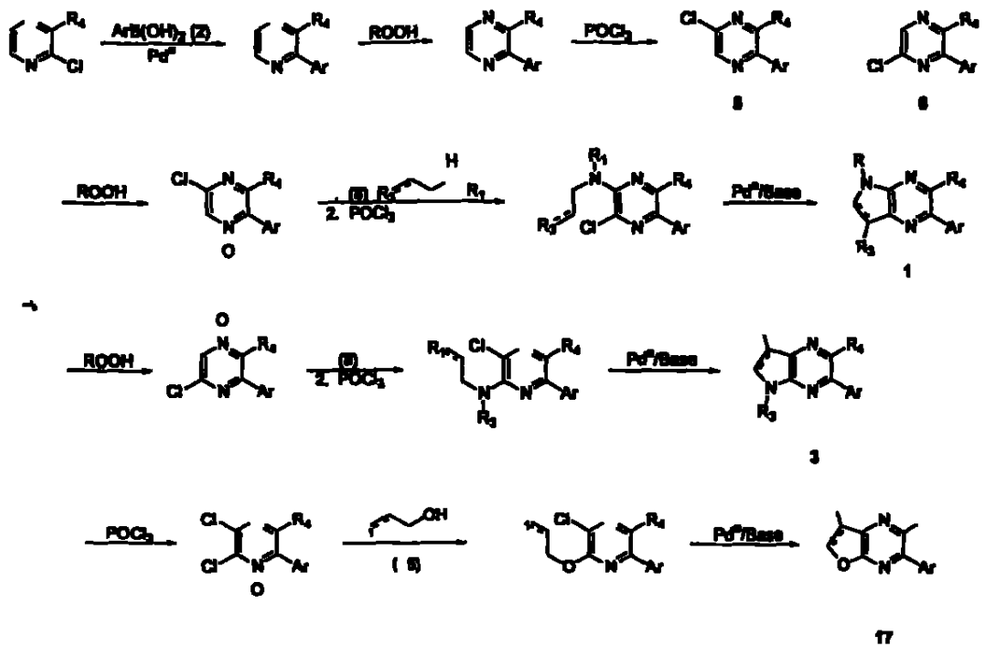
EXAMPLES

Preparation of Compo nds

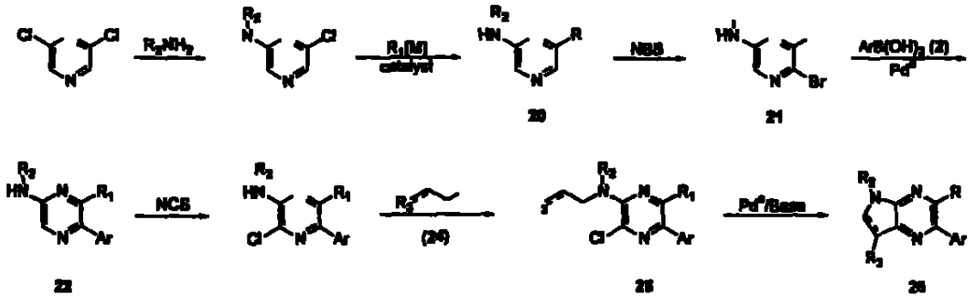
The compounds of the present nvention can be prepared in a number of ways well known to one skilled in the art of organic synthesis The compounds of the present inveption can be synthes zed using the methods descr bed below together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below Each of the references cited below are hereby incorporated herein by reference Preferred methods for the preparation of compounds of the present invention include but are not lim ted to, those described in Scheme L Those who are skilled in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention

Scheme I

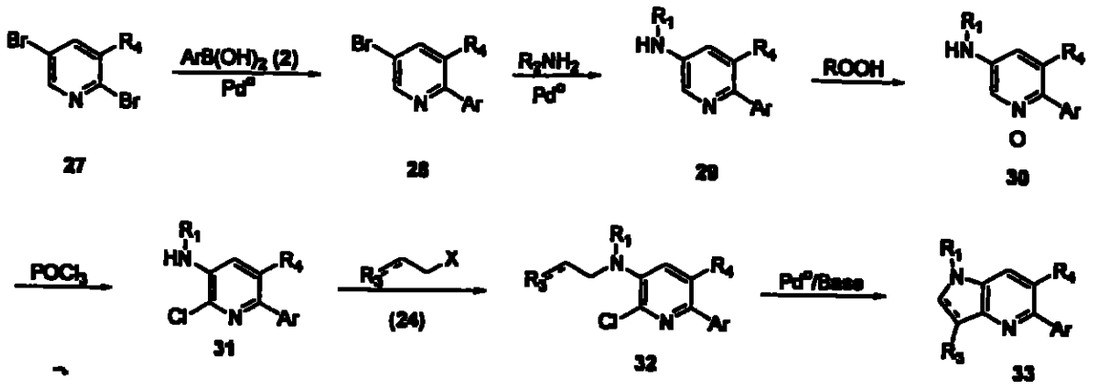
Synthesis of Pyrrolo[2,3 b]pyrazines and Furo[2 3-b]pyrazines



Scheme II

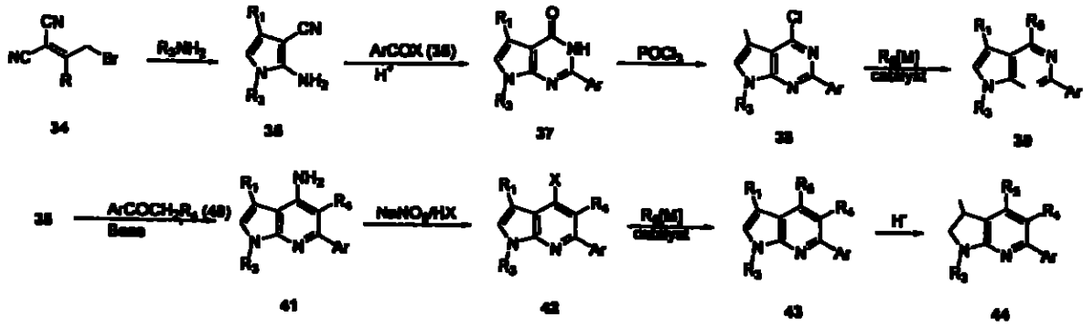


Scheme III

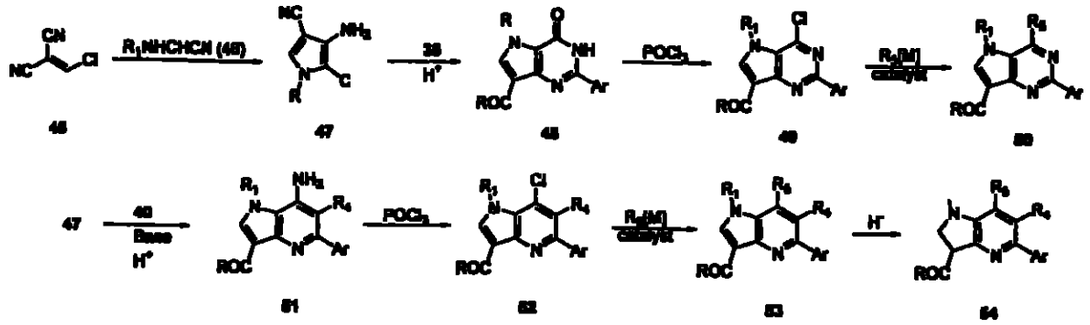


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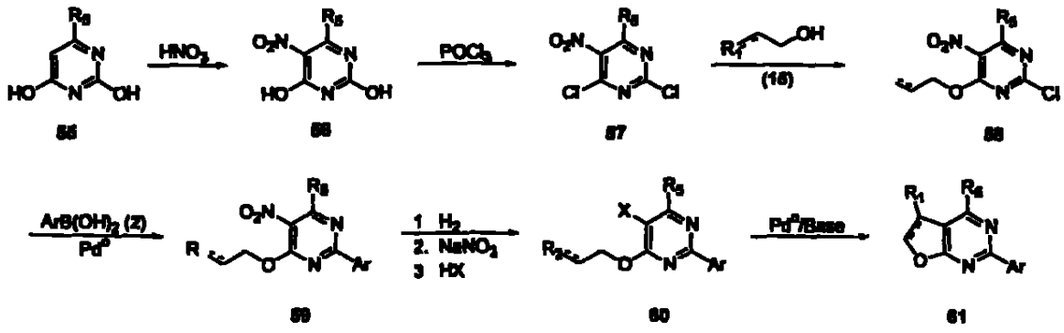
Scheme IV



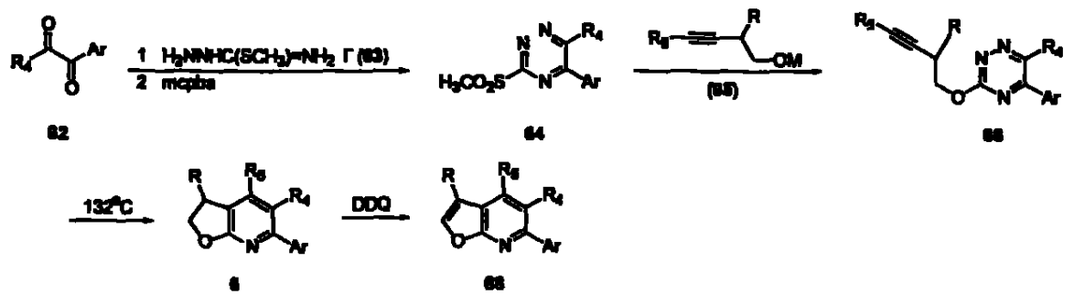
10 Scheme V



Scheme VI

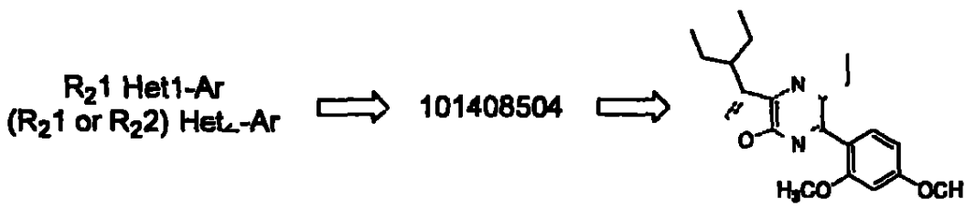


Scheme VII

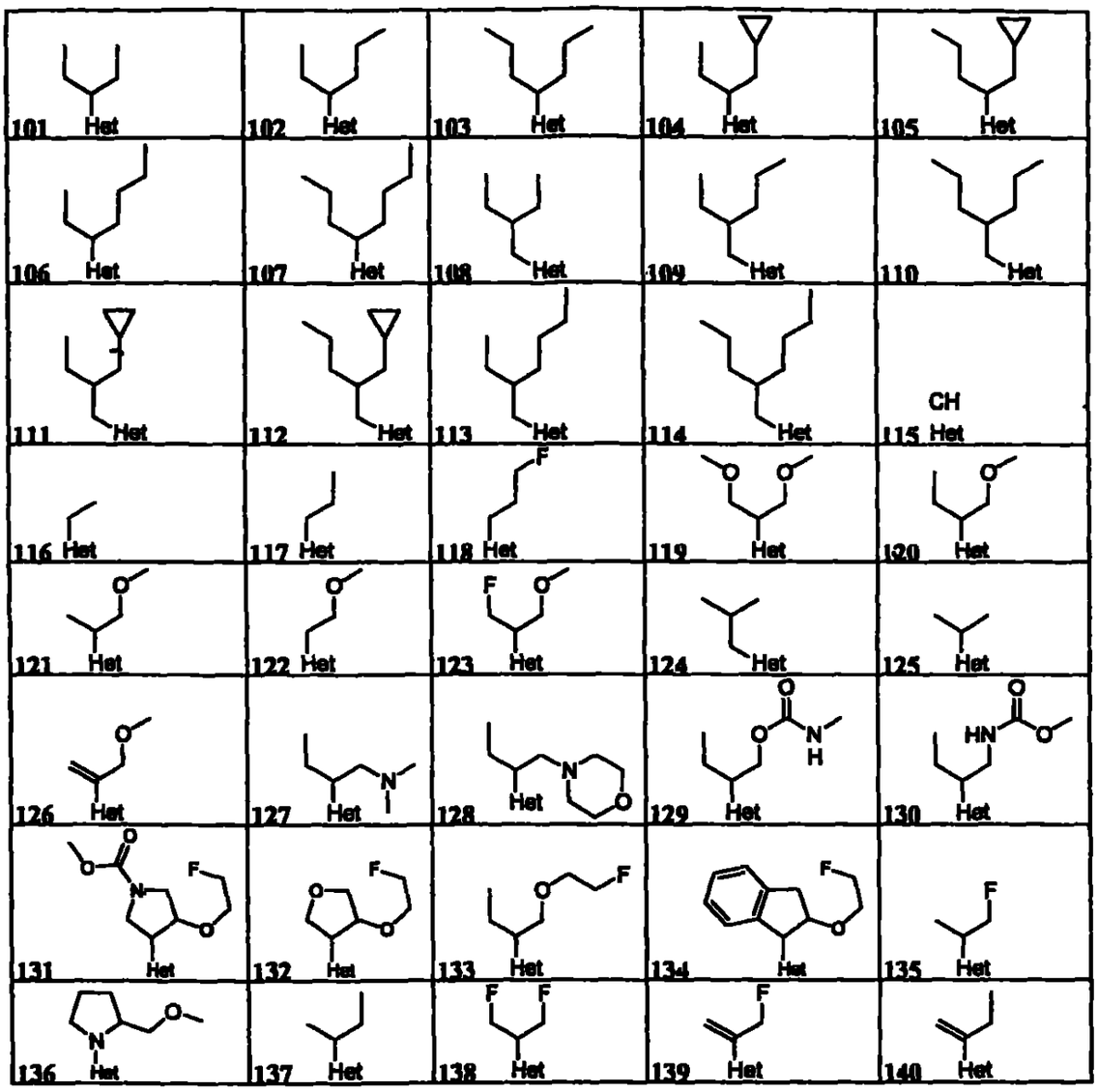


Exemplified compounds of the Invention

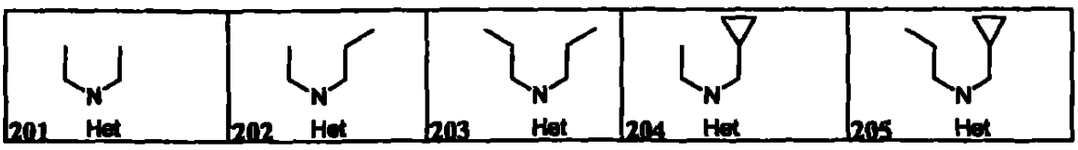
The R_21 Matrix, R_22 Matrix, Het Matrix, and Ar-Matrix tables below set forth a number of compounds of the invention which are prepared by the methods illustrated in Reaction Schemes I VII shown above Compo nds are formed by combining ny element from the R_21 Matrix or R_22 Matrix with any element from the Het matrix to form an R_21 Het or R_32 moiety and then combining this moiety with any element of the Ar Matrix to form a compound of the invention For example, the combination of lement 101 from the R_21 Matrix, with element 408 from the Het-matrix, gives the moiety 101408 This mo ety is then combined with element 504 from the Ar-matrix, to form a compo nd of the in ention compound 101408504 which is 3-(2 4-Dimethoxy-phenyl)-2-ethyl 7-(1-ethyl propyl)-furo[2 3-b]pyrazine

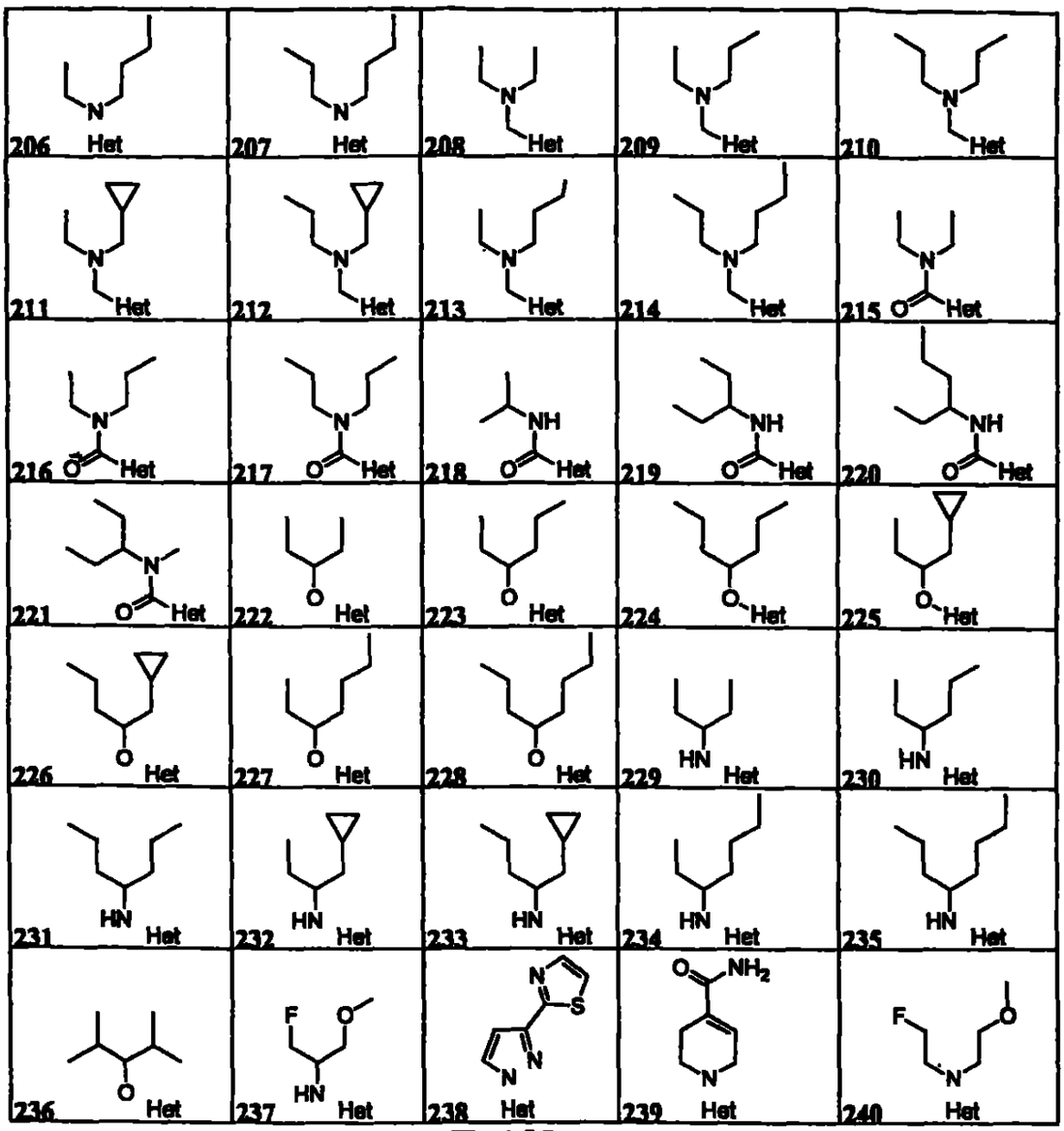


$R_2$1 Matrix

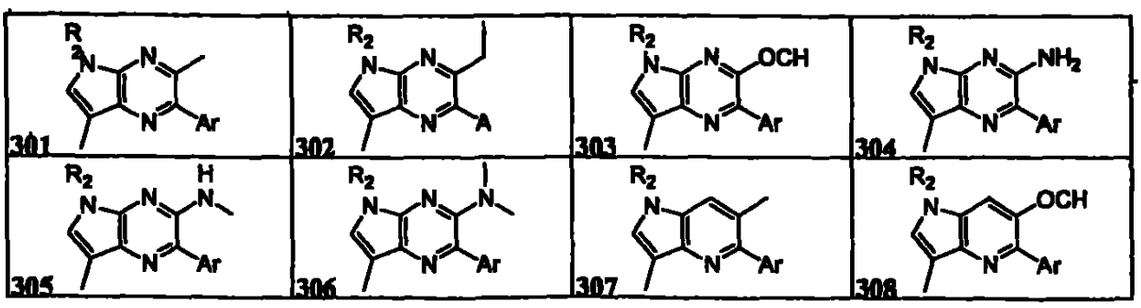


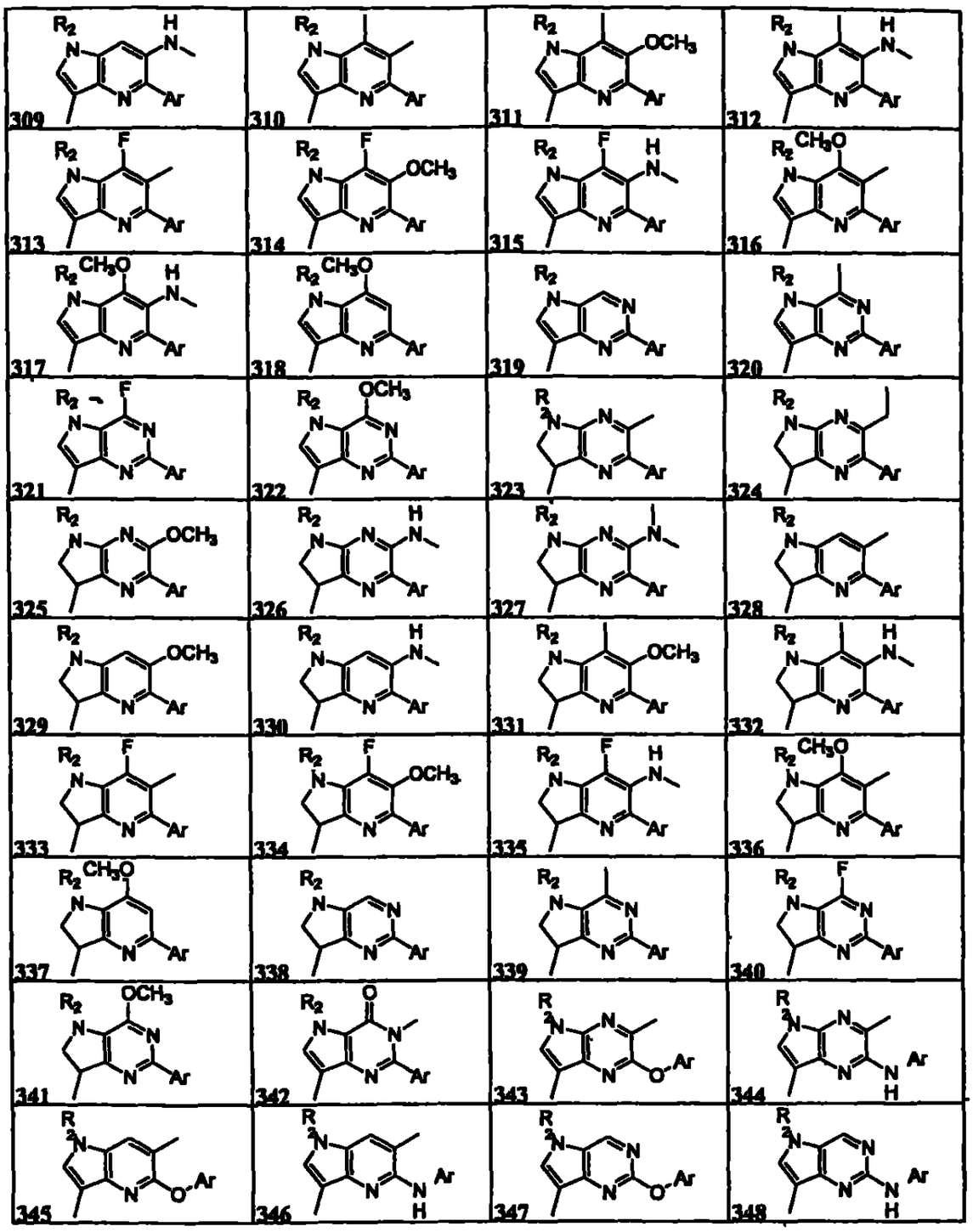
$R_2$2-Matrix



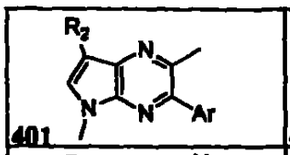
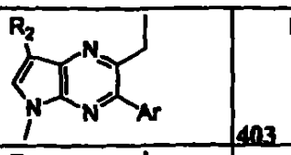
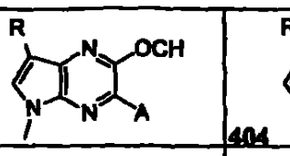
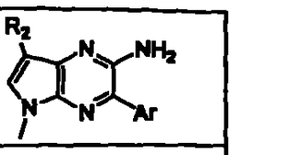
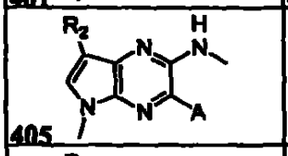
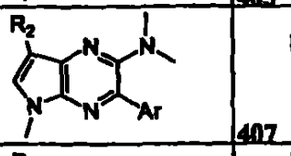
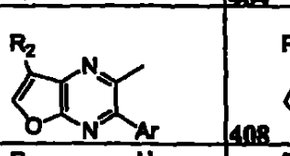
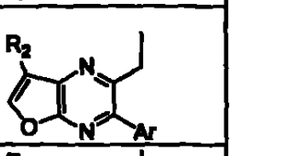
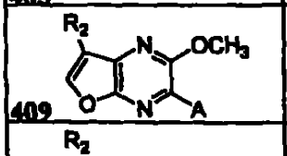
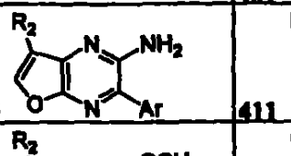
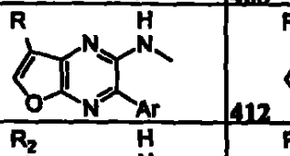
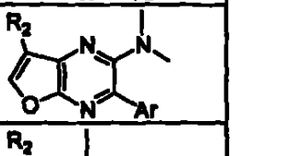
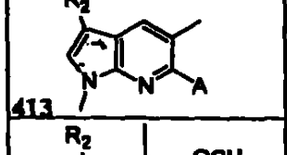
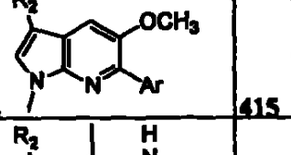
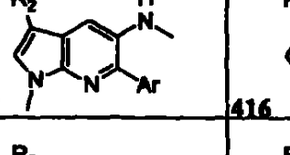
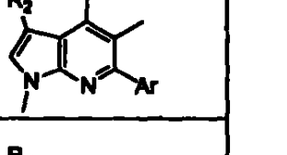
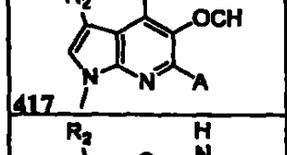
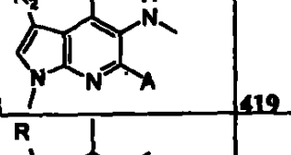
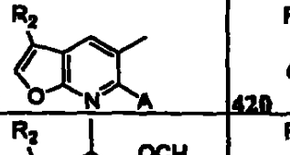
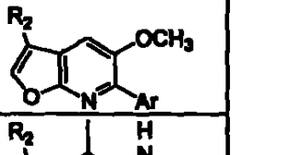
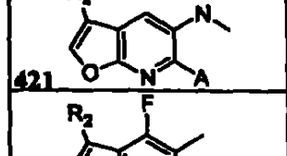
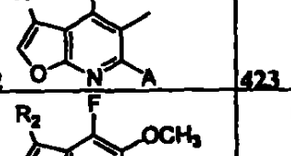
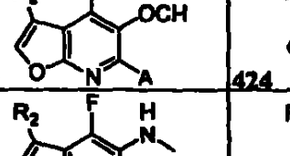
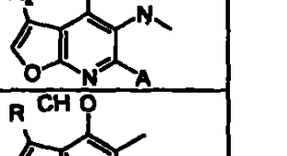
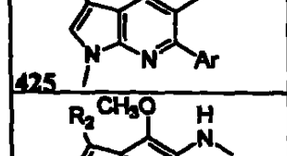
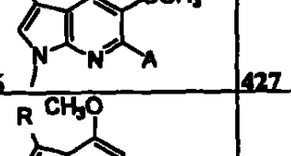
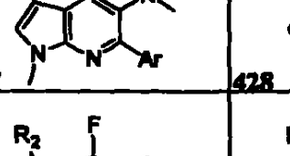
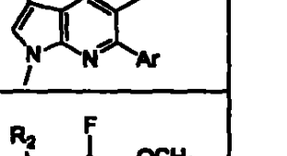
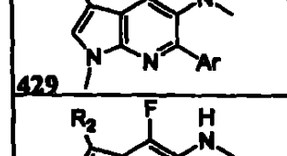
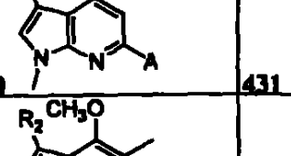
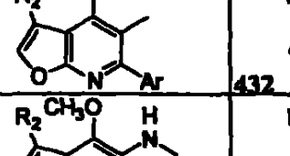
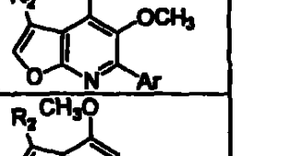
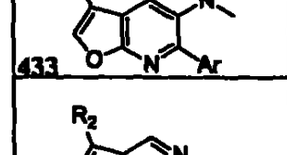
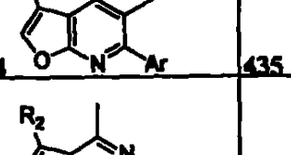
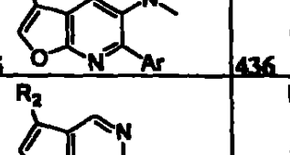
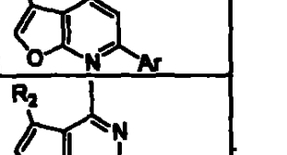
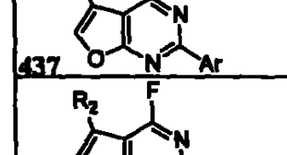
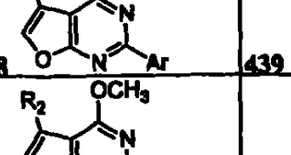
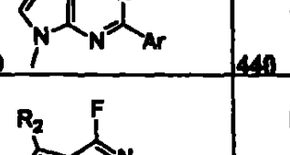
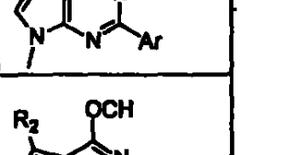
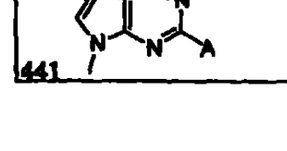
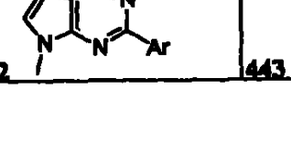
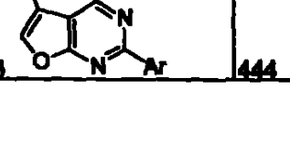
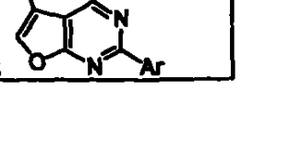

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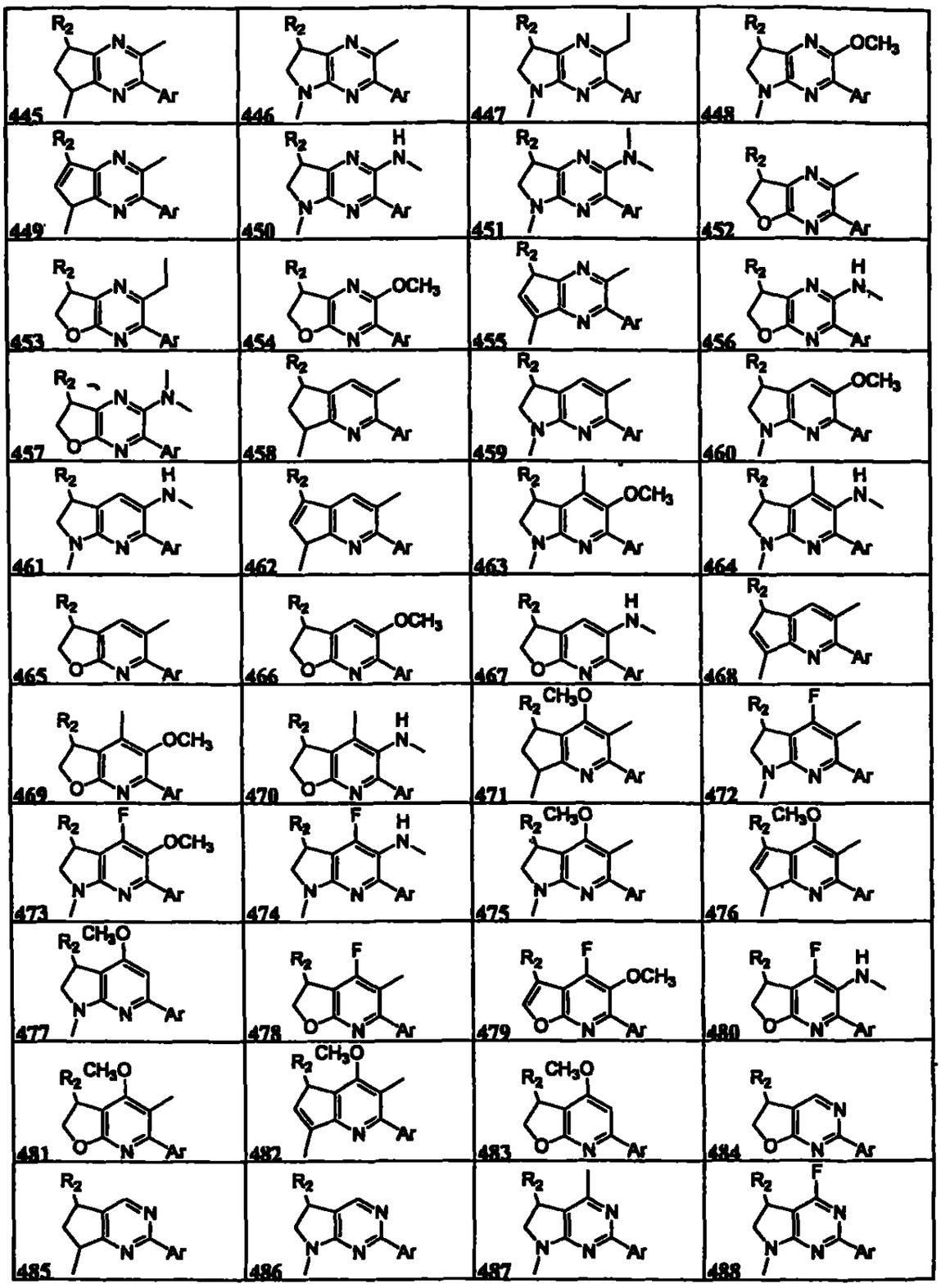
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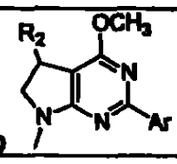
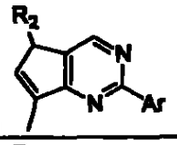
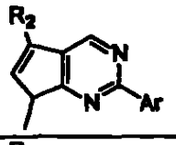
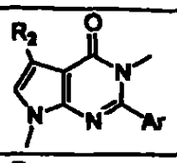
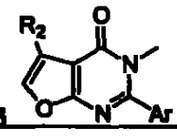
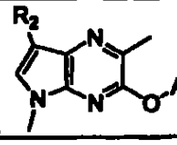
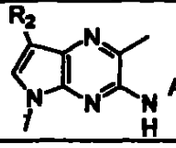
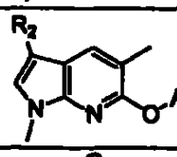
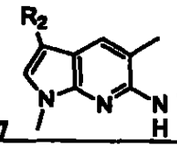
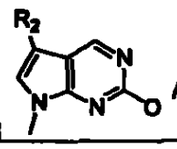
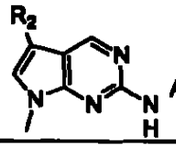
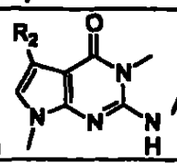

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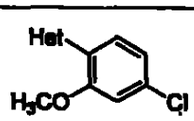
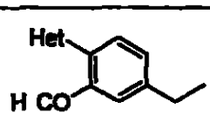
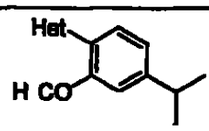
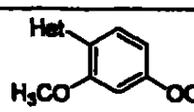
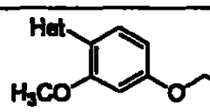
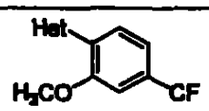
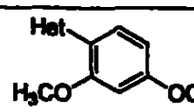
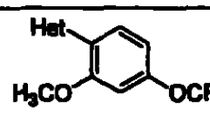
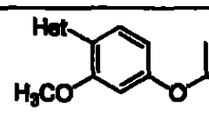
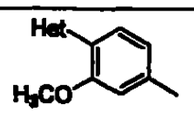
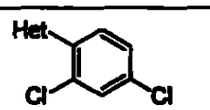
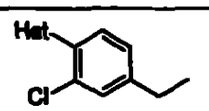
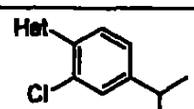
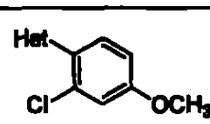
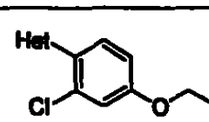
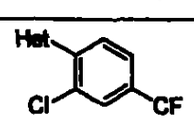
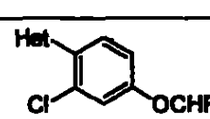
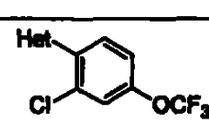
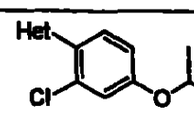
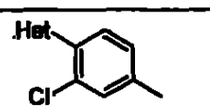
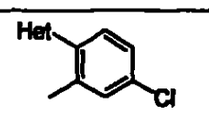
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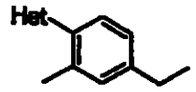
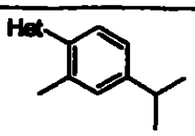
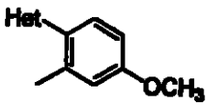
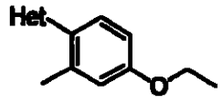
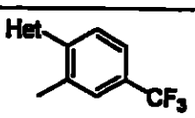
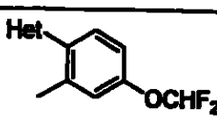
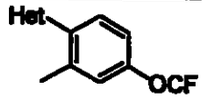
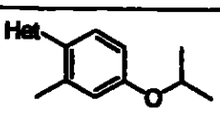
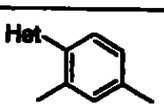
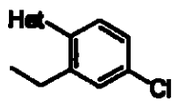
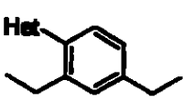
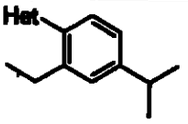
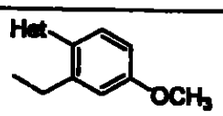
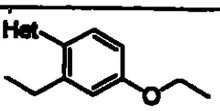
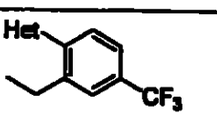
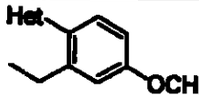
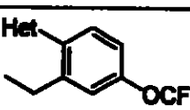
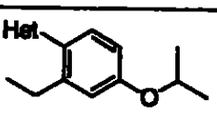
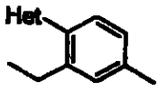
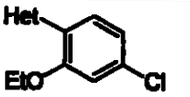
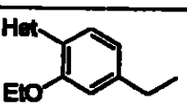
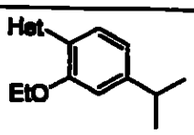
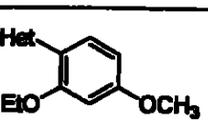
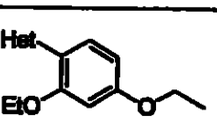
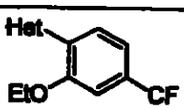
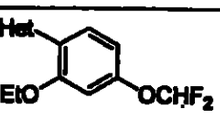
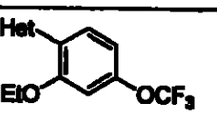
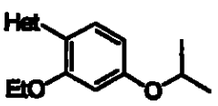
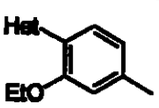
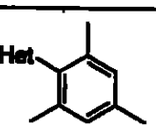
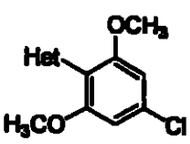
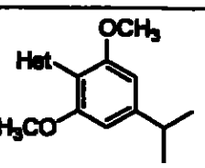
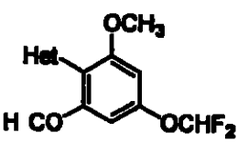
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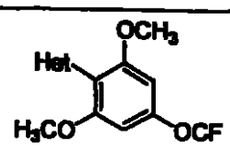
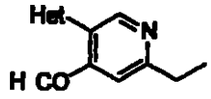
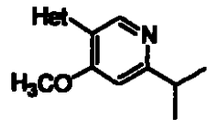
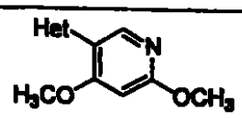
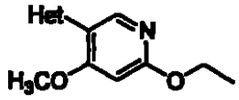
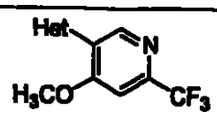
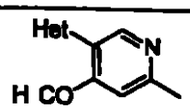
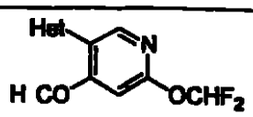
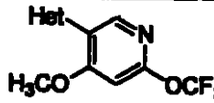
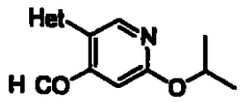
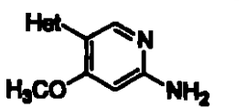
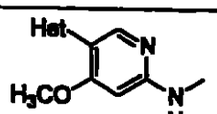
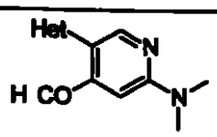
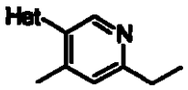
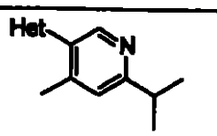
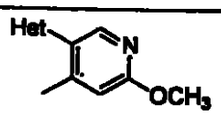
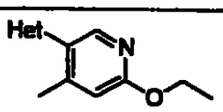
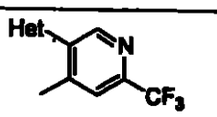
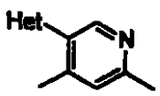
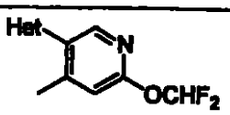
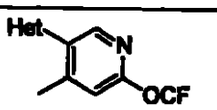
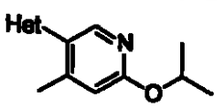
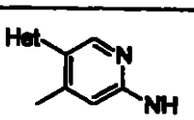
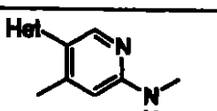
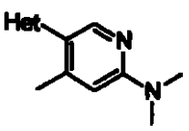
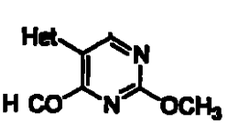
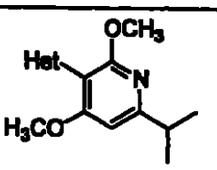
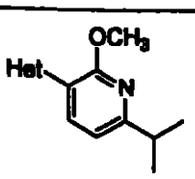
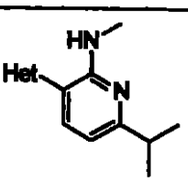
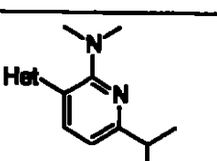

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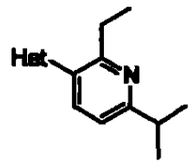
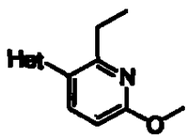
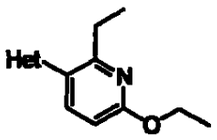
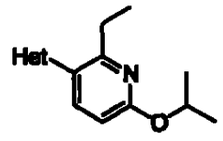
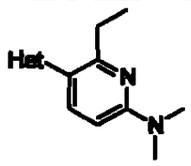
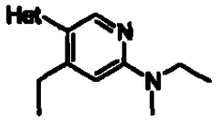
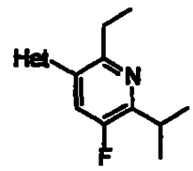
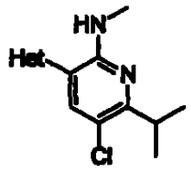
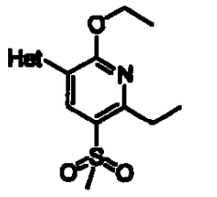
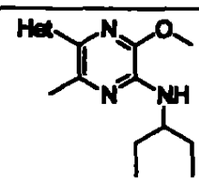
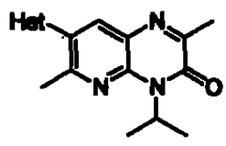
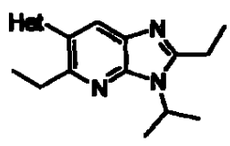
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All compounds listed below are characterized at least by ^{1}H NMR and LCMS. One of the following LCMS methods is used fo the compo nds shown below

Method 1

HPLC Instrumentation Analyses are performed using a Waters 600 series pump (Waters Corp.), a Waters 996 Diode Array detector and a Gilson 215 auto-sampler (Gilson Inc) Data are acquired using MassLynx 4 0 software with OpenLynx processing

HPLC conditions 4 6x50mm, XTerra MS C18 5 mm column (Waters Corp) UV 10 spectra/sec 220 254nm flow rate 4 0 mL/min injection volume 1 10 µl Gradient conditions – Mob le phase A 95% Water 5% Methanol with 0 05% Formic acid Mobile phase B 95% methanol, 5% Water with 0 025% Formic acid

Gradient	Time (min)	%B
	0	5
	0 01	5
	1 0	100
	2 0	100
	2 1	5

MS instrumentation LC-MS experiments are performed us ng a Waters ZMD II Mass Spectrometer

MS conditions Electrospray posit ve ion zat on cap il ry voltage 3 5kV cone voltage 30V desolvation and source temperature 250 C and 100 °C respectively mass range 120-800 with a scan time of 0 5 seconds and an inter scan delay of 0 1 min

Method 2.

Flow Injectio Condition

A Perkin Elmer HPLC system (tow Series 200 micro LC pumps, pump A and pump B with a Series 200 autosampler) is used to perform flow injection Mobile phase is a combination of 85% methanol (pump B) with 15% of water (pump A) The flow rate is 1 0 mL/min and the injection vol me is 3 µL

MS instrumentation LC-MS experiments are performed us ng a Sciex 150MA Mass Spectrometer

MS conditions Ion source s Heated Nebul zer (tmosphere pressure chemical ionizat on) The mass range is 100 1000 am Both positive and negative modes are in place For positive ion mode, Nebulizer current is 2 0 mA, and the temperature is 350 C The Nebul zer gas is 10 and the Curtain gas is 12 The decl stering potential s 30 V The Focusing potential is 200 V and the entrance potential s –10 V For negative ion mode Nebulizer current is 2 0 mA and the temperature is 350 °C The N bul zer gas is 10 a d the Curtain gas s 12 The declustering potential is 30 V The Focusing potential is 200 V and the entrance potential is 10 V

Method 3

HPLC Instrumentation HP1100 PUMP HP1100 UV detecto with 220 nm HTS/PAL autosampler from Leap Technology data acq ired by Micromass Ma

HPLC conditions Synerg 2U HYDRO-RP 20 x 4 0mm column, flow rate 1 0 mL/m n, injection volume 5 µL

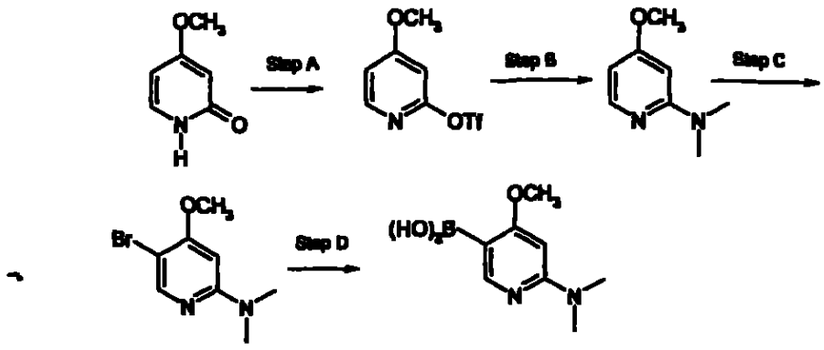
Gradient conditions 0 1% formic acid in aqueous acetonitrile 10-90% acetonitrile over 3 min then 100% acetonitrile, end at 5 min

MS instrumentation Micromass LCT TOF MS

MS conditions Scan m/z 100-1200 capillary voltage 3000V cone voltage 25V desolvation 200 °C and source temperature 100 C

EXAMPLE 1 Preparation of boronic acid intermediates

a. Synthesis of 2 (Dimethylamino)-4 methoxypyridin-5-boronic acid



Step A

To a st rred solution of 4-methoxy 1H pyridin 2-one (Walters and Shay Tetrahedron Letters 36 (1995) 7575) in methylene chloride (30 mL) at 0°C is added triflic anhydride (12 9g) followed by triethylamine (8 4g) The reaction mixture is stirred for 20 min and then allowed to warm to room temperature The volatile components are evaporated under vacuum and then the residue is dissolved in EtOAc and washed consecutively with aqueous sodium bicarbonate, water and brine solution The organic phase is separated, dried and evaporated under vac um to give trifluoro-methanesulfonic acid 4-methoxy pyridin 2 yl ester It is used n the next step without further purification

Step B

Trifluoro-methanesulfonic acid 4-methoxy-pyridin-2 yl ester (0 5g) and dimethylamine (2 4 mL of 2M in THF) are dissolved in DMSO (7mL) and warmed overn ght at 40°C EtOAc is added to the reaction mixture and it is washed with brine solution The organic phase is separated dried and evaporated under vacuum Silica gel purification gives (4-methoxypyridin 2 yl)dimethylamine It is used in the next step witho t further purification

Step C

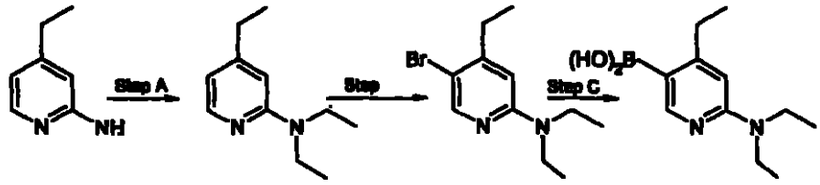
N Bromosuccinimide (1 75g) is added portionwise to a solution of (4-methoxy-pyridin-2-yl)dimethylamine (1 5g) at 0°C in chloroform (30 mL) After 30 min water (4 mL) is added to the reaction m xture and t is extracted three times with methylene chloride The combined

organic phase is separated, dried and evaporated under vacuum Silica gel purification gives (5-bromo-4-methoxy pyridin 2 yl)dimethylamine LCMS Rt 1 20 min m/z 231 03(M+H)

Step D

To a mixture of n butyllithium (2 68 mL of 1 6M in hexanes) and toluene (7 4 mL) at –65°C is added dropwise (5 bromo-4 methoxy pyridin 2 yl)dimethylamine (0 9g) in toluene (4 mL) The reaction mixture is stirred in the cold for 30 min and the THF (1 6 mL) is added a d stirring is continued for a further 15 mm Triisopropylborate (1 5g) is then added slowly and stirring is continued for 45 min The reaction mixture is then allowed to warm to room temperature overnight and 1N HCl (10 mL) s added The aqueous layer is separated and the organic phase is washed consecutively with 1N HCl and water The combined aqueous phase was adjusted to pH7 with solid sodium bicarbonate and extracted with 1 1 EtOAc/THF The organ c phase is separated dried and evaporated under vacuum to give 2-(d methylamino)-4-methoxypyridin 5 boronic ac d LCMS Rt 2 56 mm m/z 197 12(M+H)

b Synthesis f 2 (diethylam no) 4-ethylpyridin-5 boro ic acid



Step A

2 Amino-4-ethylpyridine (4 70g) is dissolved in dichloromethane (80mL) Addition of acetaldehyde (8 60mL) and stirring for 10 min is followed by addition of sodium triacetoxyborohydride (24 6g) After 1h the reaction is put into a m xture of water (300mL) and sat. sodium bicarbonate (50mL) Extraction with DCM (3x200mL) and drying over magnesium sulfate yields a crude mixture that is used in step B without any further purification LCMS m/z 179 17 (M+H)

Step B

The crude mixture from step A s dissolved in chloroform (150mL) a d cooled to 0 °C Addition of NBS (6 50g, in three port ons) is followed by stirring for 15m n The l ght yellow

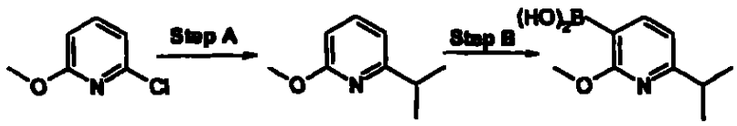
solution is then put into a mixture of water (500mL) and sat. sodium bicarbonate (100mL) Extraction with DCM (3x150mL) and drying over magnesium sulfate yields a crude mixture that is purified on silica gel LCMS m/z 257 10 (M+H)

Step C

t BuLi (50 1mL, 1 7N in pentanes) is added to THF (200mL) at 78 °C Slow addition of the purified material from step B (7 31g, in 30mL of THF) is followed by stirring for 15 min at 78 °C Upon LCMS check for unreacted bromide, triisopropyl borate (26.2mL) is added and the reaction mixture is warmed to room temperature over night. The yellowish solution is then put into a mixture of water (1000mL) and sat. sodium bicarbonate (100mL) Extraction with DCM (3x300mL) and drying over magnesium sulfate yields a crude material of good purity that can be used directly in palladium mediated couplings LCMS m/z 223 19 (M+H)

2-(Dimethylamino)-4-ethylpyridin 5-boronic acid (MS m/z 195 09 $(M+H)^+$) and 2-(ethyl methyl-amino)-4-ethylpyridin 5 boronic acid (MS m/z 209 16 $(M+H)^+$) are analogously prepared

c Synthesis of 2 isopropyl-6-methoxypyridine 3-boronic acid



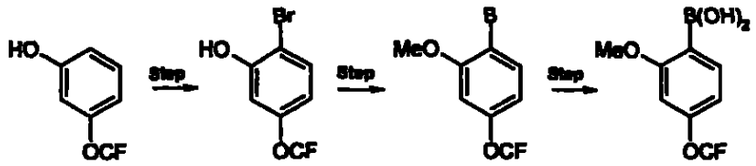
Step A

Following the procedure of Fürstner et al (JACS 124 (2002) 13856) 2-chloro-6-methoxypyridine (100g) is stirred at -30°C in a mixture of THF (2300 mL) and NMP (335 mL) $Fe(acac)_3$ (14 8g) is added, followed by isopropyl magnesium chloride (490 mL of 2M in THF) The reaction mixture is allowed to warm to 0°C over 1 hour and then saturated aqueous ammonium chloride (1000 mL) is added The aqueous phase is separated and the organic layer is washed two times w th water (1000 mL) The organic layer is distilled under reduced pressure to give 2 isopropyl-6-methoxypyridine LCMS Rt 1 95 min m/z 152 12(M+H)

Step B

2 Isopropyl-6-methoxypyridine (191 4g) and TMEDA (146 3g) are dissolved in d ethyl ether (1565 mL) and cooled to –60°C n-BuLi (760 mL of 2M) is added over 10 min and the reaction mixture is allowed to warm to room temperature over 3 5 hours The reaction m xture is chilled again to –60°C triisopropylborate (476.2g) is added and stirring is continued for 24 hours 3M HCl is then added (510 mL), followed by water (2500 mL) The aqueous phase is separated and the organic layer s washed three times with 5% aqueous NaCl (1500 mL) The four aqueous phases are sequentially extracted with diethyl ether (2000 mL) and the combined ether extracts are concentrated under vacuum to give 2 isopropyl-6-methoxypyridine-3 boronic acid LCMS Rt 2 80 min m/z 196 11(M+H)

d Synthesis of 2 methoxy-4 trifluoromethoxyphenylboronic acid



Step A

3 Trifluoromethoxyphenol (256 42g) is dissolved n dichloromethane (2000 mL) and cooled to 5 10°C under nitrogen Bromine (241 6g) is added dropwise ove 2 hours, maintaining the temperature between 5 10°C and then the cooling bath is removed Water (1000 mL) is added and the mixtue is stirred for 10 minutes and separated More water is added to the organic phase (500 mL) followed by powdered sodi m carbonate (10-12g) u til the pH is 10-11 The organic layer is separated again dried and concentrated unde vac um Dist llation affords 2 bromo-5 trifluoromethoxyphenol which is used in the next step without further purification

Step B

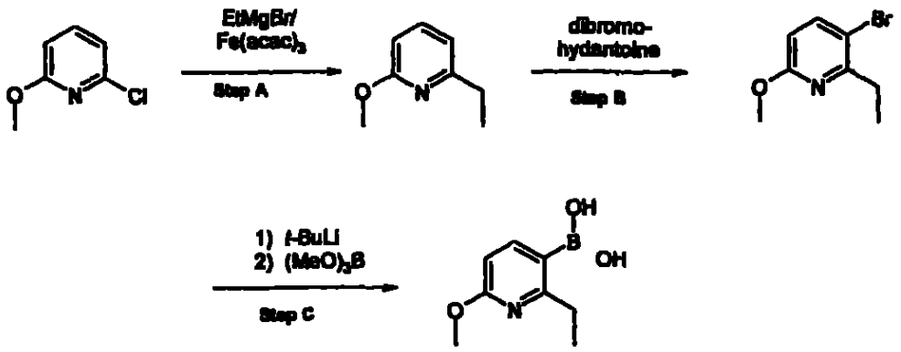
To 2 bromo-5 trifluoromethoxyphenol (479g) dissolved in toluene (2600 mL) at 1 10°C is added a solution of sodium hydroxide (80g) in water (400 mL) The reaction mixture is stirred for 20 min and then tetra n-butylammo ium brom de (24g) is added Dimethyl sulfate

(239.3g) is divided into four portions and one portion is added to the mixture every 30 min, maintaining the internal temperature around 12 15°C The reaction mixture is stirred overnight at this temperature and then water (1000 mL) is added and the organic layer is separated It is washed consecutively with water (600 mL) and brine (600 mL) and then dried and evaporated to give 3-trifluoromethoxyanisole which is used in the next step without further purification

Step C

n-Butyllithium (156 mL of 2 5 M solution in hexanes) is added under nitrogen to THF (800 mL) over a period of 5 min while maintaining the temperature between –77 and -67 °C 2-Methoxy-4-trifluoromethoxy bromobenzene (100g) is added over a 10-min period while maintaining the temperature between –76 0 and –62°C Trimethylborate (53 8 g) is added over 10 min at a temperature of –76.3 to –63 2°C After 1 hour 200 ml of 2 N hydrochloric acid (200 mL) is added to pH 1 The mixture is allowed to warm to room temperature and the organic phase is separated and concentrated under vacuum to give crude 2-methoxy-4-trifluoromethoxyphenylboronic acid The solid is treated with boiling *n*-heptane to give 2-methoxy-4-trifluoromethoxyphenylboronic acid H NMR ($CDCl_3$ 400 MHz) δ 7.89 (d, J = 8.5 Hz, 1H), 6 90 (d, J = 8 5 Hz, 1H) 6 75 (s, 1H), 6 13 (bs, 2H) 3 94 (s, 3H), Rt 2 87min m/z 281.02(M+HCOO)

e Synthesis of 2-ethyl-6-methoxy-3-pyridine boronic ac d



Step A

Commercially available 2-chloro-6-methoxypyridine is transformed into the ethyl compound as described for the corresponding 2 isopropyl-6-methoxypyridine

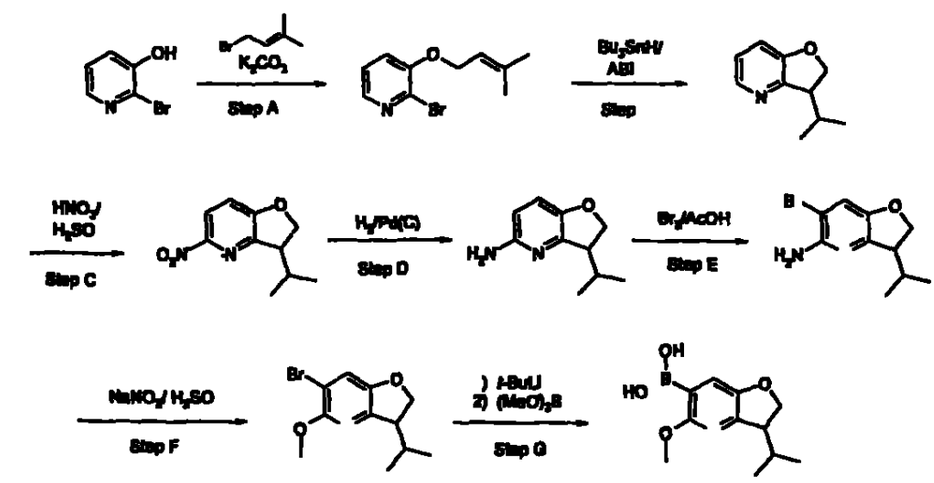
Step B

The crude mixture (30 1g) of step B is dissolved i THF (300mL) and treated with 1,3 dibromo-5 5-dimethylhydantoine (1 0-1.2eq in portions) Once TLC control shows completed conversion of the starting material the addition of the hydantoine is stopped and the mixture is put into water (1L) Extract on with DCM (3x300mL), drying over magnesium sulfate, and purification on silica gel affords the bromide LCMS m/z 215 97 (M+H)

Step C

Conversion of the bromide into the corresponding boronic acid follows the last step of the previously described synthesis of 2-diethylamino-4-ethyl 5 pyridine boron c acid with methyl borate be ng used as electrophile The resulting crude material is of good purity and can be used directly in palladium mediated coupl ngs LCMS m/z 182 05 (M+H)

f Synthesis of 3 isopropyl-5 methoxy-2 3-dihydro-furo[3 2 b]pyridine 6-boro ic acid



Step A

Commercially ava lable bromo-3 hydroxypyridine (9 41g) and 3 3-dimethylallyl bromide (9.67g) are dissolved in acetone (150mL) After addition of potassium carbonate (17 9g) the mixture is refluxed for 90min before being put into water (300mL) Extraction with DCM (4x200mL), drying o er magnesium sulfate and purif cat on on silica gel affords the allyl ether LCMS m/z 241 98 (M+H)

Step B

The ether of step A (960mg) tributyltin hydride (1.28g), and ABIN (218mg) are dissolved in toluene (20mL) and heated to 95 °C for 26h The resulting mixture is put into water (300mL) and sat. sodium bicarbonate (30mL) Extraction with DCM (3x100mL), drying over magnesium sulfate and purification on silica gel yields the bicyclus LCMS m/z 164 13 (M+H)

Step C

The cyclic ether (524mg) of step B is dissolved in conc sulfuric acid (5mL) and then cooled to 0 °C After slow addition of fuming nitric acid (1.25mL), the reaction mixture is stirred for 2h before being put onto 30 ml of ice The resulting suspension is basified (ph=10) with 10N NaOH and subsequently extracted with DCM (3x100mL) Drying over magnesium sulfate and purification on silica gel affords the desired nitro compound LCMS m/z 209 14 (M+H)

Step D

The nitro compound (622mg) of step C is dissolved in methanol (20mL) Reduction is achieved by adding a catalytic amount of Pd/C (10%) and maintaining a hydrogen atmosphere (normal pressure) for 90min Filtration through celite (10g) and concentration affords a crude mixture that is directly used in step E LCMS m/z 179 11 (M+H)

Step E

The crude mixture of step D (459mg) is dissolved in acetic acid (10mL) and then cooled to 0 °C to yield a semi frozen mixture Bromine (0 139mL) is slowly added and the reaction is stirred for another 5 min before being put into sat. sodium bicarbonate (100ml) and 1N sodium sulfite solution (20mL) Extraction with DCM (3x100mL), drying over magnesium sulfate, and purification on silica gel affords the bromide LCMS m/z 256 98 (M+H)

Step F

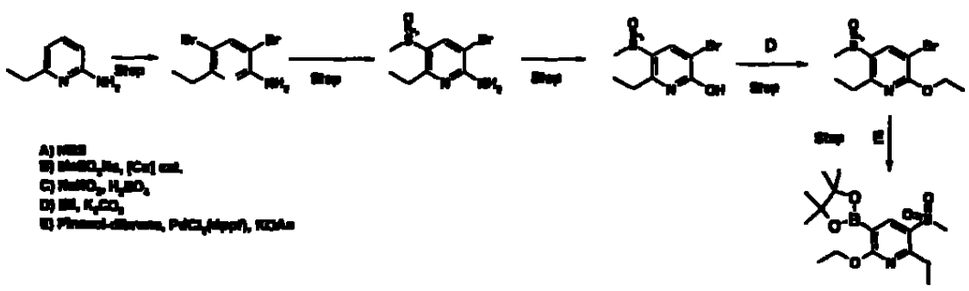
The amino bromide (500mg) of step E is dissolved in a solution of sulfuric acid in methanol (10mL 15% sulfuric acid) and then cooled to 0 °C After addition of sodium nitrite (268mg), the solution is allowed to warm to rt over a period of 16h After being put into sat. sodium bicarbonate (100mL), the aqueous layer is extracted with DCM (3x100mL) and dried over

magnesium sulfate Purification on silica gel affords the methoxy bromide LCMS m/z 272 00 (M+H)

Step G

Conversion of the bromide into the corresponding boronic acid follows the last step of the previously described synthesis of 2-diethylamino-4-ethyl 5 pyridine boronic acid with methyl borate being used as electrophile The resulting crude material is of good purity and can be used directly i palladium mediated couplings LCMS m/z 238 04 (M+H)

g Synthesis of 2-ethoxy-6-ethyl 5-methanesulfonyl 3-(4 4 5 5 tetramethyl [1 3 2]dioxaborolan-2 yl)-pyridine



Step A

A mixture of 18 8g of 6-ethyl-pyridin-2 ylamine in 400 ml CH_2Cl_2 is added NBS (55.32g) portionwise at room temperature After add tion the resulting mixture is stirred at room temperature for 10 m n before it is washed with water and brine The resulting organic phase is dried evaporated and purified by column chromatography (Hexane/EtOAc=7/1) to give desired product 3 5-dibromo-6-ethyl-pyridin 2 ylamine m/z 281 0 (M+H)

Step B

3 5 Dibromo-6-ethyl pyridin-2 ylamine (37 5g) is dissolved in anhydrous DMSO (300ml) and the mixture is degassed with N_2 for 2 min followed by addition of sodium methylsulfonate (19.5g) $(CuOTf)_2$ Ph.H (3 9g) and trans-1 2-cyclohexane-diamine (3 06g) After stirring at 110 C for 20 ho rs, the resulting mixture is diluted with water extracted with EtOAc (4x100ml), washed with brine and dried over Na_2SO After evaporation of

solvent, the residue is purified by column chromatography (Hexane/EtOAc=1/1) to give desired product 3-bromo-6-ethyl 5-methanesulfonyl-pyridin 2 ylamine m/z 281 2 (M+H)

Step C

3 Bromo-6-ethyl 5 methanesulfonyl pyridin 2 ylamine (7 88g) is dissolved in H_2SO_4 H_2O (ratio 1 6) (175ml) and the mixture is cooled to 0 °C After adding the solution of $NaNO_2$ (4 1g) in 15 ml H_2O dropwise (keep inner temperature below 5 °C) the mixture is stirred at 0 °C to room temperature for overnight. The desired product 3 bromo-6-ethyl 5 methanesulfonyl-pyridin-2-ol is collected by filtration following by washing with water (50 ml) This crude product is used for next step without further purification m/z 280 0 (M+H)

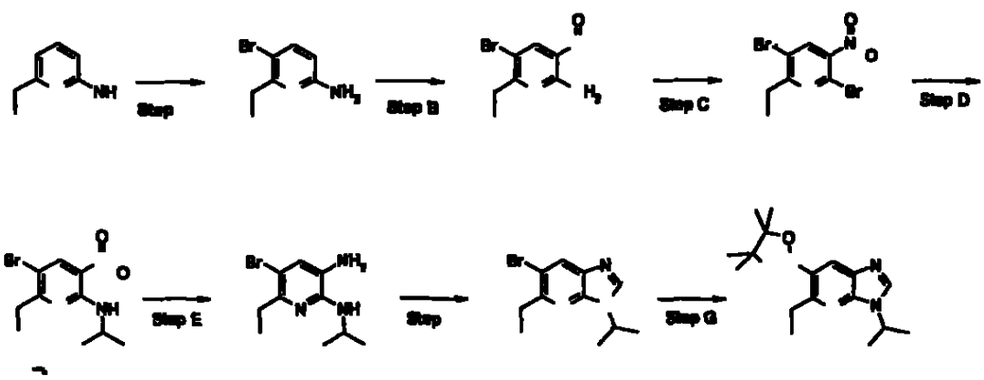
Step D

A mixture of 3-bromo-6-ethyl 5-methanesulfonyl pyridin 2-ol (15 84g) and DMF (200ml) is cooled to 0 C and K_2CO_3 (11 71g) is added followed by ethyl iodide (11.3ml) The resulting mixture is stirred at 0 °C to room temperature for overnight. After the reaction is complete, water is added and the resulting mixture is extracted with EtOAc (3x200ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The pure product 3 bromo-2-ethoxy-6-ethyl 5 methanesulfonyl-pyridine is obtained after column chromatography m/z 282 1 (M+H Et)

Step E

A mixture of 3-bromo-2-ethoxy-6-ethyl-5 methanesulfonyl-pyridine (400mg) in DMSO (20ml) is added bis(pinacolato) diboron (396mg), KOAc (382mg) and $PdCl_2$(dppf) (49mg) and the resulting mixture is stirred at 90 C for overnight. After the reaction is complete, the mixture is poured into water and extracted with ethyl acetate (3x40ml) The combined organic layers are washed with brine, dried over Na_2SO_4 Flash column chromatography purification (Hexane/EtOAc=8/1) gives the pure product 2-ethoxy-6-ethyl 5 methanesulfonyl 3-(4 4 5,5-tetramethyl [1 3,2]dioxaborolan 2 yl)-pyridine m/z 356.3 (M+H)

h. Synthesis of 5-ethyl 3 isopropyl-6-(4 4 5 5-tetramethyl [1 3 2]dioxaborolan-2 yl) 3H imidazo[4 5-b]pyridine



Step A

To a solution of 2-amino-6-ethyl-pyridine (50 g) in chloroform (250 mL) is added NBS (73 g) at 0 C over 30 min The mixture is stirred for additional 30 min and is directly purified by flash column chromatography on silica gel to give 5 bromo-6-ethyl-pyrid n-2 ylamine as white solid Rf (hexane EtOAc = 4 1) = 0.34

Step B

5 Bromo-6-ethyl pyrid n 2 ylamine (34g) is added to cH_2SO_4 (110 mL) below 10 C. To the stirred mixture is added HNO_3 (8.2 mL) below 15 C over 40 min The mixture is stirred at 0 C for 1 h at RT for 1 h and finally at 50 °C for 1 h The mixture is poured into ice-water and is basified by 50 % NaOH Yellow crystals are collected by filtration, washed with water and dried under reduced pressure to give 5 bromo-6-ethyl 3-nitro-pyridin 2 ylamine Rf (hexane EtOAc = 4 1) = 0.5

Step C

To a stirred suspension of 5 bromo-6-ethyl 3-nitro-pyridin 2 ylamine (5 g) in AcOH (20 mL) is added 48 % HBr (20 mL) below 10 °C Bromine (2 92 mL) is added to the mixture below 10 C over 15 min At 0°C a solution of $NaNO_2$ in water (3 65 g, 15 mL) is added over 20 min below 15 C The mixture is stirred at 0 C for 30 min and at RT for 1h The mixture is cooled to 0 C neutralized by 50 % of NaOH, and extracted with DCM The extract is dried over $MgSO_4$ and is concentrated under reduced pressure to give 2,5-dibromo-6-ethyl-3 nitro-pyridine as yellow oil Rf (hexane EtOAc = 9 1) = 0 7

Step D

To a stirred suspension of 2 5-dibromo-6-ethyl-3 nitro-pyridine (20 g) in EtOH (20 mL) is added a solution of isopropylamine (25 mL) in water (60 mL) at 0 °C The mixture is stirred at 0 °C for 10 min and at RT for 2 h. Red yellow crystals formed are collected by filtration and are washed with water The wet crystals are dissolved in DCM (250 mL). After drying over $MgSO_4$, the solvent is removed under reduced pressure to give (5 bromo-6-ethyl 3 nitro-pyridin-2 yl)-isopropyl-amine as red yellow solid Rf (hexane EtOAc = 9 1) = 0 77

Step E

To a solution of (5 bromo-6-ethyl 3-nitro-pyridin-2 yl)-isopropyl-amine (1 g) in EtOH (4 mL) is added conc HCl (0 05 mL) water (1 mL) and reduced iron (3 g) at RT The mixture is refluxed for 90 min The iron residue is removed by filtration and is washed with EtOH. The combined filtrates are concentrated under reduced pressure To the residue is added water and the mixture is extracted with EtOAc The combined extracts are washed with brine and dried over $MgSO_4$ The solvent is remo ed under reduced pressure to give 5 bromo-6-ethyl-N 2 isopropyl-pyridine-2 3-diamine as gum LCMS Rt 1.20 min, m/z 258 05 / 260 04 (M+H)

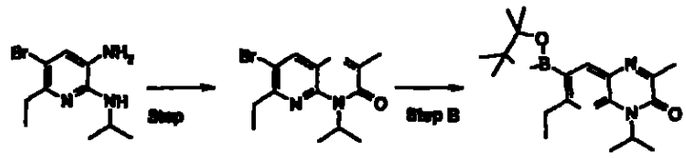
Step F

5 Bromo-6-ethyl-N 2 isopropyl pyridine-2,3-diamine (1 g) is dissolved in diethoxymethylacetate (4 mL) and is heated at 120 C for 90 min After cooling to RT the mixture is directly purified by flash column chromatography on silica gel to giv 6-bromo-5 ethyl-3 isopropyl-3H imidazo[4 5 b]pyridine as colorless o l Rf (hexane EtOAc = 2 1) = 0 32

Step G

To a solution of 6-bromo-5-ethyl 3 isopropyl 3H imidazo[4 5-b]pyridine (59 mg) in DMSO (2 mL) is added bis(pinacolate)diborane (69 mg) KOAc (65 mg) and $PdCl_2$(dppf)-DCM complex (9 mg) at RT The mixture is stirred at 90 C for 20 h to give 5-ethyl 3 isopropyl-6-(4 4,5 5-tetramethyl [1 3 2]dioxaborolan-2 yl)-3H im dazo[4 5 b]pyridine wh ch is able to be used for the coupling LCMS Rt 1 66 min, m/z 316.22 (M+H)

i Synthesi of 6-Ethyl-4-isopropyl 2 methyl 7 (4 4 5 5-tetramethyl [1 3 2]dioxaborolan-2 yl) 4H pyrido[2 3-b]pyrazin-3-one



Step A

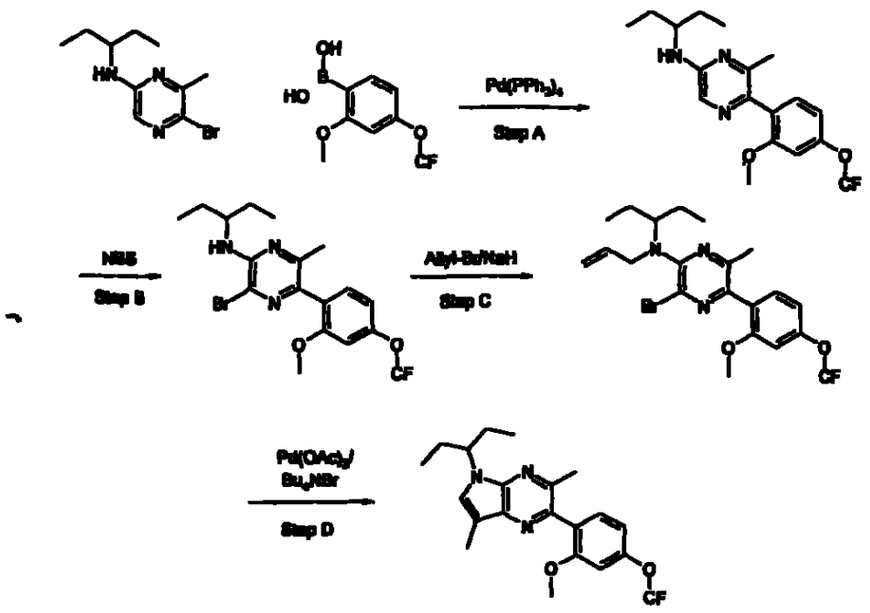
To a solution of 5-bromo-6-ethyl N 2 isopropyl pyrid ne-2 3-diamine (2 38 g) in toluene (10 mL) is added ethyl pyruvate (2 05 mL) at RT The mixture is refluxed for 18 h and is poured into water and is extracted with EtOAc The extract is washed with brine and is dried over $MgSO_4$ After removal of the solvent under reduced pressure the residue is purified by flash column chromatography on sil ca gel to g ve 7 bromo-6-ethyl-4-isopropyl 2 methyl 4H pyrido[2 3 b]pyrazin 3-one as white crystal LCMS Rt 1 74 min m/z 310 02 / 312 02 (M+H)

Step B

To a solution of 7 bromo-6-ethyl-4-isopropyl 2 methyl-4H pyrido[2,3 b]pyrazin 3-one (0 2 g) in DMSO (4 mL) is added bis(p nacolate)diborane (0 2 g) KOAc (0 19 g) and $PdCl_2$(dppf) DCM complex (29 mg) at RT The m xture is stirred at 90 C for 20 h to give 6-ethyl-4-isopropyl 2-methyl 7-(4 4 5,5 tetramethyl [1 3 2]dioxaborolan-2-yl)-4H pyrido[2 3 b]pyrazin-3-one, which is able to be used for the coupling LCMS Rt 1 80 m n m/z 358.22 (M+H)

EXAMPLE 2

Synthesis of 5-(1-ethyl-propyl)-2-(2-methoxy-4-trifluoromethoxy phenyl)-3 7-dimethyl-5H pyrrolo[2,3-b]pyrazine



Step A

The previously described 2-bromo-3 methyl-5-*iso*pentylaminopyrazine (870mg) and the literature known 2-methoxy-4 trifluoromethoxyphenyl boronic acid (796mg) are dissolved in DME (15mL) After degassing, tetrakis(triphenylphosphine)palladium (0) (390mg) is added A second degassing is followed by addition of a 1N sodium carbonate solution (6 74mL) whereupon the reaction is heated to 80 C for 6h The yellowish mixture is then put into water (200mL) extracted with DCM (3x100mL) and dried over magnesium sulfate Purification on silica gel affords the coupled product. LCMS m/z 370 17 (M+H)

Step B

The product (205mg) of step A is dissolved in chloroform (10mL) and NBS (99mg) is added After being stirred for 10 min, the yellowish mixture is put into water (100mL) extracted with DCM (3x100mL) and dried over magnesium sulfate Purification on silica gel affords the bromide LCMS m/z 448 11 $(M+H)^+$

Step C

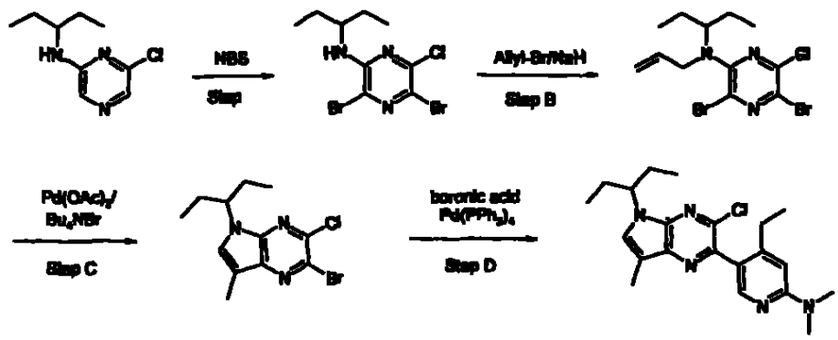
The bromide (173mg) of step B and allyl bromide (0 33mL) are dissolved in DMF (5mL) Sodium hydride (100mg) is added and the reaction is stirred for 10min at rt. The mixture is then put into water (100mL) and extracted with ethyl ether (2x100mL) The combined organic layers are washed with water (50mL), dried over magnesium sulfate and purified on silica gel to afford the allylated amino-compound LCMS m/z 488 11 (M+H)

Step D

The allyl compound (138mg) of step C tetrabutylammonium bromide (91mg), palladium acetate (6 4mg), and potassium carbonate (117mg) are dissolved in DMF (5mL) After heating to 80 °C for 90 min the mixture is worked up according to step C Final purification on s lica gel affords the title compound LCMS m/z 408 21 (M+H)

EXAMPLE 3

Synthesi f {5-[3-chloro-5-(1-ethyl-propyl)-7 methyl-5H pyrrolo[2,3-b]pyrazin-2-yl]-4-ethyl-pyridin 2-yl}-dimethyl-amine



Step A

The pre iously described 2-chloro-6 *iso*pentylam nopyrazine (25 1g) s dissolved in chloroform (450mL) and NBS (47 1g) is added in portions After being stirred for 30 min, the yellowish mixture is put into water (400mL) and sat sodium bicarbonate (100mL), extracted with DCM (3x200mL) and dried over magnesium sulfate The crude material is carried on to step B without any further purification Rf = 0 57 in hex/ethyl acetate (10/1)

Step B

The crude material (28 37g) of step A and allyl bromide (20 6mL) are dissolved in DMF (200mL) Sodium hydride (4 76g) is added in portions and the reaction is stirred for 5h at rt. The mixture is then put into water (500mL) and extracted with ethyl acetate/hexane (1/20 3x300mL) The combined organic layers are dried over magnesium sulfate and purified on silica gel to afford the allylated product. LCMS m/z 395 85 (M+H)

Step C

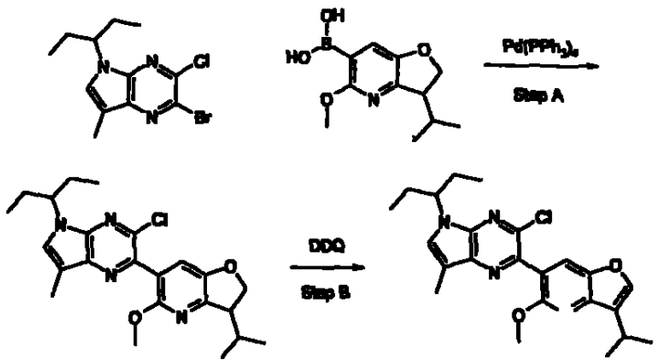
The allyl compound (23.36g) of step B, tetrabutylammonium bromide (19.00g), palladium acetate (1 32g), and potassium carbonate (24 8g) are dissolved in DMF (200mL) After heating to 80 °C for 20 min the mixture is put into water (500mL) and extracted with ethyl acetate/hexane (1/4 3x300mL) The combined organic layers are washed with water (100mL), dried over magnesium sulfate and purified on sil ca gel to afford the Heck-product. LCMS m/z 316 01 (M+H)

Step D

The Heck product of step C (1 5g) and the previously described 2-dimethylamino-4-ethyl 5 pyridine boronic acid (1.38g) are dissolved in DME (30mL) After degass ng, tetrakis(tr phenylphosphine)palladium (0) (550mg) is added A second degassing is followed by addition of a 1N sodium carbonate solution (9 5mL) whereupon the reaction is heated to 80 °C for 16h The yellowish mixture is then put into water (200mL) extracted with DCM (3x100mL) and dried over magnesium sulfate Purification on silica gel affords the title compound LCMS m/z 386.20 (M+H)

EXAMPLE 4

Synthesis of 3-chloro-5-(1-ethyl-propyl)-2-(3-isopropyl-5-methoxy furo [3,2-b]pyridin-6-yl)-7 methyl-5H pyrrolo[2,3-b]pyrazine



Step A

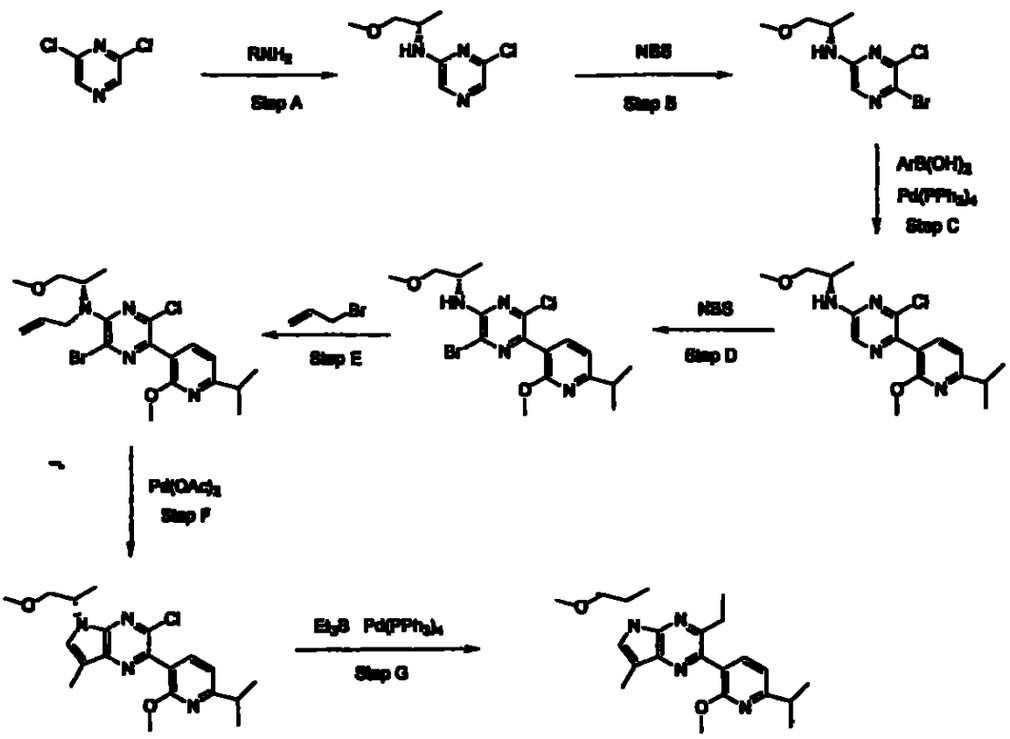
The previously described bromide (85mg) and the also previously described pyridine boronic acid (64mg) are dissolved in DME (3mL) After degassing, tetrakis(triphenylphosphine)palladium (0) (31mg) is added A second degassing is followed by addition of a 1N sodium carbonate solution (0 54mL) whereupon the reaction is heated to 80 °C for 16h The yellowish mixture is then put into water (100mL) extracted with DCM (3x100mL), and dried over magnesium sulfate Purification on silica gel affords the coupled product. LCMS m/z 429 08 (M+H)

Step B

The Suzuki product (52mg) of step A and DDQ (41mg) are dissolved in benzene (5mL) and heated to 80 °C for 3h The reaction mixture is then put into water (100mL) extracted with DCM (3x100mL) and dried over magnesium sulfate Purification on silica gel affords the title compound LCMS m/z 427 12 (M+H)

EXAMPLE 5

Synthesis of (S)-3-chloro-2-(6- isopropyl-2-methoxy pyridin-3 yl)-5-(2-methoxy 1 methyl-ethyl)-7 methyl-5H pyrrolo[2,3-b]pyrazine and (S)-3-ethyl-2-(6-isopropyl 2-methoxy pyridin-3-yl)-5-(2 methoxy 1 methyl-ethyl)-7 methyl-5H pyrrolo[2,3-b]pyrazine



Step A

2 6 Dichloropyrazine (11 7g) (S)-(+)-1-methoxy 2 propylamine (7g) and Et_3N (15 mL) in EtOH (100 mL) are heated at 105 °C for 2 days. The mixture is evaporated and dissolved in EtOAc and washed with sat. $NaHCO_3$, H_2O and dried Evaporation affords 2-chloro-6-[(S)-1 methoxy-2-propyl]aminopyrazine LCMS m/z 202.3 and 204 3 (M+H)

Step B

2-Chloro-6-[(S)-1 methoxy 2-propyl]aminopyrazine (8.3g) is dissolved in $CHCl_3$ (250mL) Upon addition of NBS (7.33g) the reaction mixture is stirred at 25 °C for 30 min. Subsequently the crude mixture is evaporated dissolved in EtOAc/hexane (1 4 500mL) washed with water and dried over sodium sulfate Purification on silica gel affords 3-bromo-2-chloro-6-[(S)-1 methoxy-2-propyl]aminopyrazine LCMS m/z 280.2 282.2 and 284.2 (M+H)

Step C

3 Bromo-2-chloro-6-[(S) 1-methoxy 2-propyl]aminopyrazine (10 7g) and 2 methoxy-6-isopropyl 3 pyridineboronic acid (9 7g) are dissolved in DME (250mL) After 10min of degassing, tetrakis(triphenylphosphine)palladium(0) (2 2g) is added, followed by 1 min of

degassing. Upon addition of an aqueous 1N sodium carbonate solution (76mL), the reaction mixture is heated at 90 °C for 12h. Subsequently the crude mixture is put into water (800mL), extracted with EtOAc/hexane (1:1, 3x250mL) and dried over sodium sulfate. Purification on silica gel affords 3-{2-chloro-6-[(S)-1-methoxy-2-propyl]aminopyrazin-3-yl}-2-methoxy-6-isopropylpyridine. LCMS m/z 351.3 and 353.3 (M+H).

Step D

3-{2-Chloro-6-[(S)-1-methoxy-2-propyl]aminopyrazin-3-yl}-2-methoxy-6-isopropylpyridine (4.85g) is dissolved in $CHCl_3$ (60mL). Upon addition of NBS (2.46g) the reaction mixture is stirred at 25 °C for 30 min. Subsequently the crude mixture is evaporated, dissolved in EtOAc/hexane (1:4, 250mL), washed with water and dried over sodium sulfate. Purification on silica gel affords 3-{5-bromo-2-chloro-6-[(S)-1-methoxy-2-propyl]aminopyrazin-3-yl}-2-methoxy-6-isopropylpyridine. LCMS m/z 429.2, 431.2 and 433.2 (M+H).

Step E

3-{5-Bromo-2-chloro-6-[(S)-1-methoxy-2-propyl]aminopyrazin-3-yl}-2-methoxy-6-isopropylpyridine (4.3 g) is dissolved in DMSO (50 ml). Upon addition of NaH (60%, 0.8g), the reaction mixture is stirred at 25 °C for 30 min before allyl bromide (1.7 mL) is added. The reaction mixture is stirred at 25 °C for 2h. Subsequently the crude mixture is put into water (250mL), extracted with EtOAc/hexane (1:4, 2x250mL), and dried over sodium sulfate. Purification on silica gel affords 3-{5-bromo-2-chloro-6-[(S)-N-allyl-1-methoxy-2-propyl]aminopyrazin-3-yl}-2-methoxy-6-isopropylpyridine. LCMS m/z 469.3, 471.3 and 473.3 (M+H).

Step F

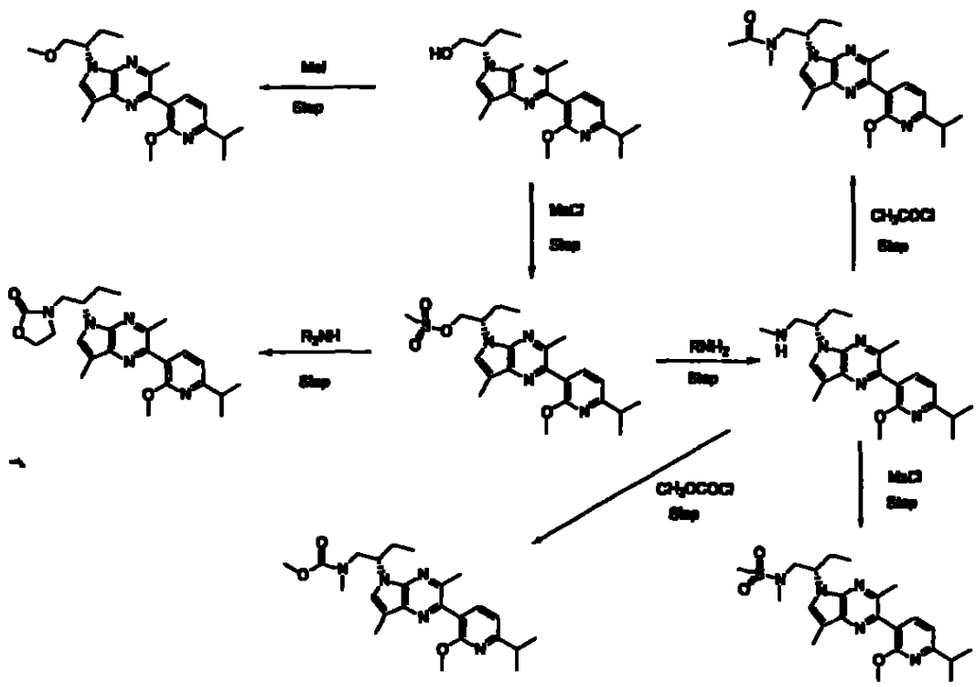
3-{5-Bromo-2-chloro-6-[(S)-N-allyl-1-methoxy-2-propyl]aminopyrazin-3-yl}-2-methoxy-6-isopropylpyridine (4.6g) is dissolved in DMF (80mL). After 10min of degassing, $Pd(OAc)_2$ (225mg) is added, followed by 1 min of degassing. Upon addition of potassium carbonate (4.1 g) and Bn_4NBr (4.0g) the reaction mixture is heated at 90 °C for 1h. Subsequently the crude mixture is put into water (500mL), extracted with EtOAc/hexane (1:2, 3x150mL) and dried over sodium sulfate. Purification on silica gel affords (S)-3-chloro-2-(6-isopropyl-2-methoxy-pyridin-3-yl)-5-(2-methoxy-1-methyl-ethyl)-7-methyl-5H-pyrrolo[2,3-b]pyrazine. LCMS m/z 389.4 and 391.4 (M+H).

Step G

(S)-3-Chloro-2-(6-isopropyl 2-methoxy-pyridin 3 yl)-5-(2 methoxy 1 methyl-ethyl)-7 methyl-5H-pyrrolo[2,3-b]pyrazine (400mg) is dissolved in toluene (5mL) After 10min of degassing, tetrakis(triphenylphosphine)palladium(0) (35mg) is added, followed by 1 min of degassing Upon addition of triethylborane (1N in hexane, 3 mL) and aqueous 1N sodium carbonate solution (2mL) the reaction mixture is heated at 110 C for 36h Subsequently the crude mixture is put into water (10mL), extracted with EtOAc/hexane (1 3 3x25mL), and dried over sodium sulfate Purification on silica gel affords (S)-3-ethyl-2-(6-isopropyl 2 methoxy pyridin 3 yl)-5-(2-methoxy-1-methyl-ethyl)-7-methyl 5H pyrrolo[2,3-b]pyrazine LCMS m/z 383.4 (M+H)

EXAMPLE 6

Synthesis of methanesulfonic acid 2-[(S)-2-(6-isopropyl 2 methoxy pyridin-3-yl)-3 7 dimethyl pyrrolo[2,3-b]pyrazin-5-yl]-butyl ester 3-{2-[(S)-2-(6-isopropyl-2 methoxy pyridin-3-yl)-3 7-dim thyl pyrrolo[2,3-b]pyrazin-5-yl]-b tyl}-oxazolidin 2-one, {2-[(S)-2-(6-isopropyl-2-methoxy-pyridin-3-yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin-5-yl] butyl}-methyl-amine, N {2-[(S)-2-(6-isopropyl-2-methoxy-pyrid n-3-yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin-5-yl] butyl} N methyl-acetamide, N {2-[(S)-2-(6-isopropyl-2-methoxy pyridin-3-yl)-3 7-dimethyl-pyrrolo[2,3-b]pyraz n-5-yl] b tyl}-N methyl-methanesulfonamide {2-[(S)-2-(6-isopropyl-2-methoxy pyridin-3-yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin-5-yl] butyl} methyl-carbamic acid methyl ester and (S)-2-(6-isopropyl-2-methoxy pyridin-3-yl)-5-(1 methoxymethyl-ropyl)-3 7-dimethyl-5H pyrrolo[2,3-b]pyrazin



Step A

2-[(S)-2-(6-Isopropyl-2 methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazi 5 yl] butan 1-ol (275 mg) is dissolved in CH Cl_2 (6mL) MsCl (0 07 mL) and Et_3N (0 16mL) are added at r t and the mixture is stirred for 1h The mixture is evaporated and dissolved in EtOAc/hexane (1 1) and washed with sat. $NaHCO_3$, H_2O and dried Evaporation affords the methanesulfonate LCMS m/z 447 1 (M+H)

Step B

2-Oxazolidone (26 mg) is dissolved in DMF (3mL) NaH (12 mg, 60%) is added at t and the mixture is stirred for 10 min at 85 °C Upon addition of the methanesulfonate from step A (35mg), the reaction mixture is heated at 85 °C for 3h Subsequently the mixture is poured into H_2O and extracted with EtOAc Evaporation and purification on silica gel affords 3 {2 [(S) 2-(6 isopropyl-2 methoxy pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl] butyl}-oxazolidin 2-one. LCMS m/z 438 4(M+H)

Step C

The above methanesulfonate (120mg) from step A, LiI (150mg) and methylamine (7M in NMP 2mL) are heated at 90 °C for 4h. Subsequently the crude mixture is put into water (10mL), extracted with EtOAc (2x15mL), and dried over sodium sulfate Purification on silica gel affords {2 [(S) 2-(6-isopropyl 2-methoxy pyridin 3 yl)-3 7-dimethyl-pyrrolo[2, 3-b]pyrazin-5-yl]-butyl} methyl-amine LCMS m/z 383.3 (M+H)

Step D

{2 [(S) 2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl-pyrrolo[2, 3-b]pyrazin 5 yl]-butyl} methyl-amine (30mg) is dissolved in CH_2Cl_2 (1 mL) Acetyl chloride (0 017 mL) and Et_3N (0 033 mL) are added The resulting reaction mixture is stirred at r t. for 30 min Subsequently the crude mixture is put into water (2mL), extracted with EtOAc (2x5mL), washed w th sat. $NaHCO_3$ (2 mL) and dried over sodium sulfate Purification on silica gel affords N {2-[(S)-2-(6-isopropyl 2 methoxy pyridin-3 yl)-3 7 dimethyl-pyrrolo[2,3 b]pyrazin-5 yl]-butyl} N methyl-acetamide LCMS m/z 424.5 (M+H)

Step E

{2 [(S) 2-(6-Isopropyl 2 methoxy-pyridin-3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl] butyl} methyl-amine (20mg) is dissolved in CH_2Cl_2 (1 mL) Methanesulfonyl chloride (0 008 mL) and Et_3N (0 021 mL) are added The resulting reaction mixture is stirred at r t. for 30 min Subsequently the crude mixture is put into water (2mL), extracted with EtOAc (2x5mL) washed with sat. $NaHCO_3$ (2 mL) and dried over sodium s lfate Purification on silica gel affords N {2-[(S)-2-(6-isopropyl 2-methoxy pyridin 3 yl) 3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl]-butyl} N methyl-methanesulfonamide LCMS m/z 460 3 (M+H)

Step F

{2 [(S)-2 (6-Isopropyl 2 methoxy pyridin-3 yl)-3 7-dimethyl pyrrolo[2 3-b]pyrazin-5-yl]-butyl} methylamine (20mg) is dissolved in CH_2Cl_2 (1 mL) Methyl chloroformate (0 012 mL) and Et_3N (0 013 mL) are added. The resulting reaction mixture is stirred at r t for 30 min Subsequently the crude mixture is put into water (2mL), extracted with EtOAc (2x5mL), washed with sat. $NaHCO_3$ (2 mL) and dried over sodium sulfate Purification on silica gel affords {2 [(S)-2-(6-isopropyl 2-methoxy-pyridin 3 yl)-3 7

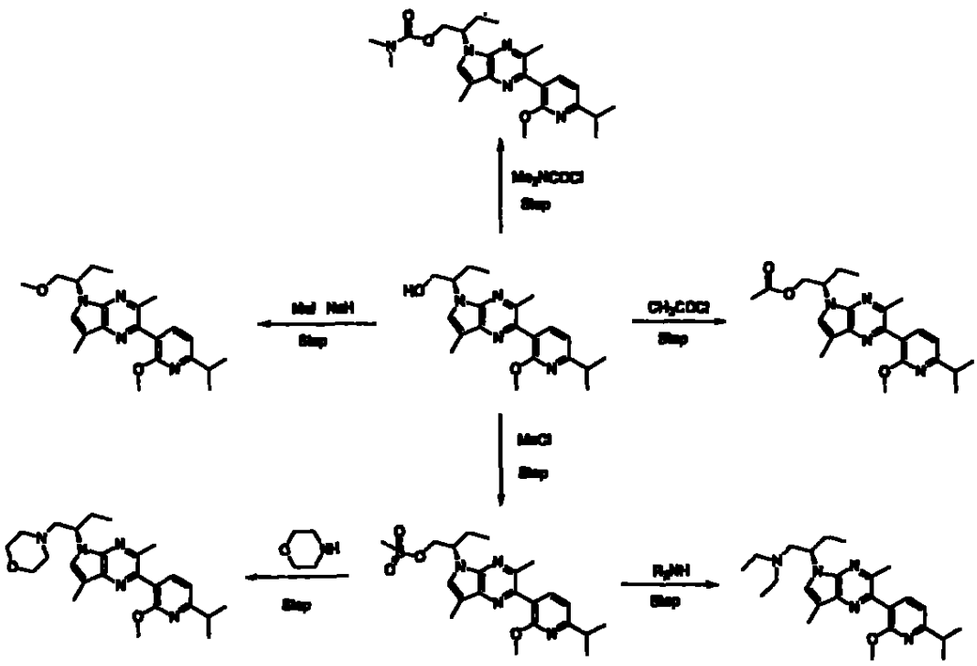
dimethyl-pyrrolo[2 3 b]pyrazin-5 yl]-butyl}-methyl-carbamic acid methyl ester LCMS m/z 440 4 (M+H)

Step G

2 [(S) 2-(6-Isopropyl 2-methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin-5 yl] butan 1-ol (40 mg) is dissolved in DMF (1mL) NaH (60%, 7 mg) is added followed by CH_3I (0 02mL) at r t. and the mixture is stirred for 1h The mixture is evaporated and dissol ed in EtOAc/hexane (1 1) and washed with sat $NaHCO_3$ H_2O and dried E aporation affords (S)-2-(6 isopropyl 2 methoxy-pyridin-3 yl)-5-(1 methoxymethyl ropyl)-3 7 dimethyl 5H pyrrolo[2,3 b]pyrazine LCMS m/z 383.2 (M+H)

EXAMPLE 7

Synthes s of (R)-2-(6-isopropyl 2-methoxy pyr din-3-yl)-3 7-d methyl-5-(1 morpholin-4-ylmethyl propyl)-5H pyrrolo[2,3-b]pyrazine, diethyl-{2-[(R)-2-(6-isopropyl-2-m thoxy pyridi -3-yl)-3 7-dim thyl-py rol [2,3-b]pyrazin-5-yl] butyl}-amine, (R)-2-(6-isopropyl-2 m thoxy pyridin-3 yl)-5-(1 methoxymethyl-propyl)-3 7-dimethyl-5H pyrrol [2,3-b]py az ne, acetic acid 2-[(R)-2-(6-isopropyl-2-methoxy pyridin-3-yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin-5-yl] b tyl ester and dimethylca bam c acid 2-[(R)-2-(6-isopropyl 2-methoxy pyridi -3-yl)-3 7-dimethyl-pyrrolo[2,3-b]py azin-5-yl] butyl ester



Step A

2 [(R)-2-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3-b]pyrazin 5 yl] butan 1-ol (275 mg) is dissolved in CH_2Cl_2 (6mL) MsCl (0 07 mL) and Et_3N (0 16mL) are added at r t and the mixture is stirred for 1h The mixture is evaporated and dissolved in EtOAc/hexane (1 1) and washed with sat. $NaHCO_3$ H_2O and dried Evaporation affords the methanesulfonate LCMS m/z 447 1 (M+H)

Step B

The above methanesulfonate (95mg), LiI (50mg) and morpholine (0.35mL) are heated at 90 °C for 4h Subsequently the crude mixture is put into water (10mL), extracted with EtOAc (2x15mL) and dried o er sod ium sulfate Purification on silica gel affords (R)-2-(6-isopropyl-2-methoxy-pyridin 3 yl)-3 7-dimethyl 5-(1-morpholin-4-ylmethyl-propyl)-5H pyrrolo[2,3-b]pyrazine LCMS m/z 438 5 (M+H)

Step C

The above methanesulfonate (115mg), L I (50mg) and diethylamine (0 5mL) in CH_3CN (3mL) are heated at 90 C for 4h Subsequently the crude mixture is put into water (10mL), extracted with EtOAc (2x15mL), and dried over sodium sulfate Purification on silica gel affords diethyl {2-[(R)-2-(6 isopropyl 2-methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl] butyl}-amine LCMS m/z 424 14 (M+H)

Step D

2 [(R) 2-(6-Isopropyl 2 methoxy-pyridin-3 yl)-3 7-dimethyl pyrrolo[2,3-b]pyrazin 5 yl]-butan 1-ol (185mg) is dissolved in DMF (2mL) NaH (60%, 40 mg) is added, followed by CH_3I (0 1mL) at r t. and the resulting mixture is stirred for 1h The mixture is evaporated and dissolved in EtOAc/hexane (1 1) and washed with sat $NaHCO_3$ H_2O and dried. Evaporation affords (R) 2-(6-isopropyl 2-methoxy-pyridin 3 yl)-5-(1 methoxymethyl propyl)-3 7 dimethyl 5H-pyrrolo[2 3 b]pyrazine LCMS m/z 383.2 (M+H)

Step E

2 [(R)-2-(6-Isopropyl-2 methoxy-pyridin 3 yl)-3 7-dimethyl-pyrrolo[2,3 b]pyrazin 5 yl] butan 1-ol (37mg) is dissolved in CH_2Cl_2 (1 mL) Acetyl chloride (0 015 mL) and Et_3N

(0 028 mL) are added The resulting reaction mixture is stirred at r t. for 30 min Subsequently the crude mixture is put into water (2mL), extracted with EtOAc (2x5mL), washed with sat $NaHCO_3$ (2 mL) and dried over sod um sulfate Purification on s lica gel affords acetic acid 2 [(R)-2-(6-isopropyl-2-methoxy-pyridin-3-yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin 5 yl] butyl ester LCMS m/z 411 4 (M+H)

Step F

2-[(R)-2-(6 Isopropyl 2 methoxy-pyridin-3 yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin 5 yl] butan 1-ol (70mg) is dissolved i CH_2Cl_2 (2 mL) Dimethylcarbamyl chloride (0 08 mL) and pyridine (0 2 mL) are added The resulting reaction mixture is stirred at 75 °C overnight Subsequently the crude mixture is put into water (2mL), extracted with EtOAc (2x10mL) washed with sat $NaHCO_3$ (4 mL) and dried over sodium sulfate Purification on silica gel affords dimethylcarbamic acid 2-[(R)-2-(6-isopropyl-2-methoxy-pyridin-3-yl)-3 7-d methyl pyrrolo[2,3 b]pyrazin 5 yl] butyl ester LCMS m/z 440 4 (M+H)

To a solution of the above nitro compound (2 63g) in ether (30mL) is added $SnCl_2x2H_2O$ (6.54g) in conc HCl (20mL)) dropwise at room temperature After the addition is completed, the reaction mixture is stirred at room temperature for 1h The reaction mixture is basified with 10N NaOH (cooled with ice-bath) to pH 9~10 After extracting with ether (200mLx3), the combined ether-layers are dried over Na_2SO_4 to give a crude mixture that is used in step B without any further purification ^{1}H NMR ($CDCl_3$, δppm) 7.26 (1H d, J = 8.3 Hz) 6 93 (1H, s), 6 89 (1H, d, J = 8 3 Hz), 6 79 (1H, s), 4 03(2H, brs), 3 78 (3H, s) 2 05 (3H, s)

Step B

To a solution of the crude product (166mg) from step A in DMSO (2ml) is added NaH (60%, 60mg) The reaction mixture is stirred at rt for 2h, followed by addition of 3-bromopentane (226mg) After being stirred at rt for 30min, the yellowish mixture is quenched with water and extracted with EtOAc The organic layer is washed with water twice, then brine to be finally dried over Na_2SO_4 The crude product is purified on silica gel ^{1}H NMR ($CDCl_3$, δppm) 7.26 (1H d, J = 8 3 Hz) 6 87 (1H, d J = 8 3 Hz), 6 77 (1H, s), 6 76 (1H, s) 4 13 (1H, d, J = 8 6 Hz), 3 74 (3H, s) 3.24~3.29 (1H, m) 2 07 (3H, s) 1 59 1 69 (2H, m), 1.49~1 59 (2H, m) 0 97 (6H, t, J = 7.3 Hz)

Step C

To a solution of the alkylation product of step B (403mg) in NMP (2mL) and tetrabutylammonium bromide (cat.) is added NaH (60%, 120mg) The reaction mixture is stirred at rt for 2h followed by addition of allyl bromide (2 eq) After being stirred at 60 °C for 3h, the mixture is quenched with water extracted with EtOAc and dried over Na_2SO_4 The crude product is purified on silica gel ^{1}H NMR ($CDCl_3$, δppm) 7.29 (1H, d, J = 8.2 Hz), 7 17 (1H, s) 6 86 (1H, d J = 8.2 Hz), 6 76 (1H, brs), 5 66~5 75 (1H, m), 5 18 (1H, d, J = 18Hz) 5 05 (1H, d J = 10Hz) 3 77~3 81 (5H, CH_2 CH_3), 3 32 (1H m) 2 07 (3H s) 1 54 1 63 (4H, m), 0 95 (6H, t, J = 7 5 Hz)

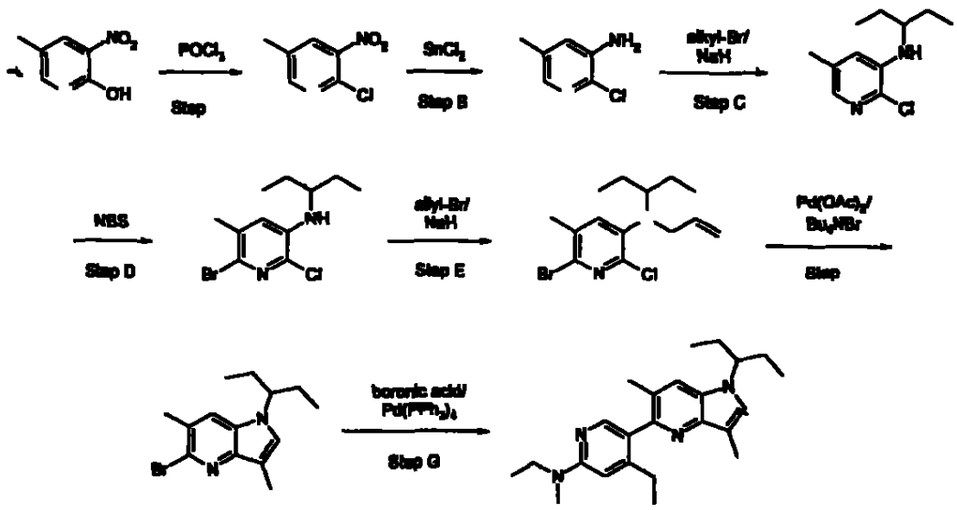
Step D

A mixture of the allylamine of step C (100mg), $Pd(OAc)_2$ (5 1mg), tetrabutylammonium bromide (72 9mg) and K_2CO_3 (93mg) in DMF (3mL) is degassed and then heated to 80 °C overnight The mixture is subsequently quenched with water extracted with EtOAc and dried over Na_2SO_4 Pur fication on silica gel yields the title compound ^{1}H NMR ($CDCl_3$,

δppm) 7 43 (1H, s), 7.35 (1H, d J = 8.3 Hz) 7 08 (1H, d, J = 1 0 Hz), 6 91–6 94 (1H dm), 6 80 (1H brs), 3 99 (1H, m), 3 77 (3H s), 2 40(3H s), 2.21 (3H s), 1 85 1 91 (4H m) 0 80 (6H brs)

EXAMPLE 10

Synthesis of ethyl {4-ethyl-5-[1-(1-ethyl-propyl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridin 5-yl] pyridi 2-yl}-methyl-amin



Step A

The shown nitropyridine (25g) in $POCl_3$ (100mL) is refluxed for 8h After completed reaction, the reaction mixture is concentrated at reduced pressure to dryness Ice (100g) is added to the residue, which is then neutralized with 2N NaOH Extract on with EtOAc (200mLx2) and drying over $MgSO_4$ yields a crude product which is used in step B without any further purificat on

Step B

To a solution of the chloro compound from step A (20g) in ethanol (300mL) is added $SnCl_2x2H_2O$ (132g) portionwise After the addition is completed the mixture is stirred for an additional 2h at 50 °C before the solvent s removed under reduced pressure DCM (400mL) is added and the suspension is neutralized with 10N NaOH and then filtered through celite

The filtrate is washed with water brine, and finally dried over $MgSO_4$ to yield the amine The crude mixture is used in step C without any further purification

Step C

To a solution of the amine (13 5g) from step B in NMP (80mL) is added tetrabutylammonium bromide (0.3g) and NaH (60%, 7 6g) at 0 °C After being stirred at rt for 3h, 3 bromopentane (1 5 eq) is added The reaction mixture is then stirred for an additional 2h before being quenched with water and extracted with EtOAc The organic layer is washed with water brine and dried over $MgSO_4$ Evaporation under reduced pressure yields a crude product which is used in step D without any further purification ^{1}H NMR ($CDCl_3$ δppm) 7 48 (1H, s) 6 67 (1H, s), 4 07 (1H, d, J = 8 2Hz) 3.2~3.24 (1H, m), 2.23 (3H s), 1 48 1 68 (4H, m), 0 93 (6H, t, J = 7 3 Hz)

Step D

The crude material of step C (3 0g) is dissolved in $CHCl_3$ (20mL) and NBS (2 63g) is added at room temperature After being stirred at rt for 30 min, the reaction mixture is washed with water brine and dried over Na_2SO_4 before it is purified on silica gel to yield the bromide ^{1}H NMR ($CDCl_3$, δppm) 6 74 (1H, s), 4 04 (1H, d J = 7 8Hz), 3 17~3.22 (1H m), 2.29 (3H, s), 1 47 1 56 (2H, m) 1 56-1 66 (2H, m), 0.93 (6H, t, J = 7 4 Hz)

Step E

To a solution of the brom de from step D (3 66g) in NMP is added tetrabutylammonium bromide (0 1g) and NaH (60%, 1 0g) at rt. After being stirred at rt for 3h, allyl bromide (3 0g) is added and the reaction mixture is stirred for an additional 4h The reaction mixture is then quenched with water and extracted with EtOAc The organic layer is washed with water brine and dried over $MgSO_4$ to yield a crude product, which is used in step F without any further purification H NMR ($CDCl_3$, δppm) 7 11 (1H, s) 5 56 5 66 (1H, m) 5 13 (1H, d J = 17 4Hz), 5 13 (1H, d, J = 10Hz) 3 70-3 72 (2H, m) 3.22~3 26 (1H, m) 2.29 (3H s), 1.52 1 60 (4H, m) 0 91 (6H, t, J = 7 4Hz)

Step F

The crude material of step E (4 1g), $Pd(OAc)_2$ (275mg), tetrabutylammonium bromide (4 5g), and K_2CO_3 (5 1g) are d ssolved in DMF (20mL) After degassing, the mixture is heated to 80

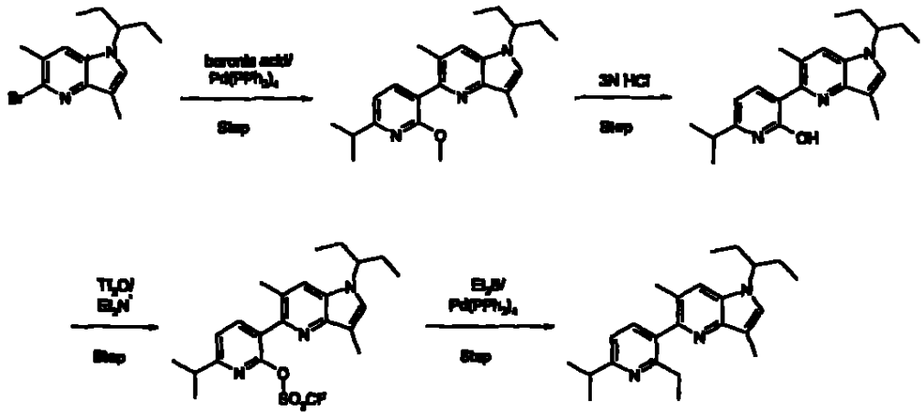
°C overnight. The black solution is then diluted with EtOAc before being washed with H_2O brine, and dried over $MgSO_4$. Purification on silica gel yields the bicyclic compound ^1H NMR ($CDCl_3$, δ ppm) 7.43 (1H, s), 7.05 (1H, s), 3.89-3.92 (1H, m), 2.48 (3H, s), 2.36 (3H, s), 1.76-1.88 (4H, m), 0.72 (6H, t, J = 7.3 Hz)

Step G

The bicyclic material of step F (118mg), $Pd(PPh_3)_4$ (70mg) and the previously described 4-ethyl-2-ethylmethylamino-3-pyridine boronic acid (104mg) are dissolved in toluene (10mL). Upon addition of 2N Na_2CO_3 (4mL), the mixture is degassed and then heated overnight to 80 °C. Subsequently the mixture is diluted with EtOAc and washed with H_2O brine, and finally dried over $MgSO_4$. Purification on silica gel yields the title compound ^1H NMR ($CDCl_3$ δ ppm) 8.00 (1H, s), 7.43 (1H, s), 7.07 (1H, brs), 6.45 (1H, s), 3.96-4.01 (1H, m), 3.62 (2H, q J = 7.0 Hz), 2.48 (3H, s), 3.06 (3H, s), 2.42 (2H, q J = 7.5 Hz), 2.39 (3H, s), 2.23 (3H, s), 1.81-1.90 (4H, m), 1.18 (3H, t, J = 7.2 Hz), 1.03 (3H, t, J = 7.5 Hz), 0.81 (6H, t, J = 7.3 Hz)

EXAMPLE 11

Synthesis of 5-(2-ethyl-6-isopropyl-pyridin-3-yl)-1-(1-ethyl-propyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine



Step A

The previously described bicyclic bromide (590mg), the also previously described 6-isopropyl-2-methoxy-3-pyridine boronic acid (507mg), and $Pd(PPh_3)_4$ (115mg) are dissolved in toluene (30mL). Upon addition of 2N Na_2CO_3 (6mL), the mixture is degassed and then heated overnight to 85 °C. Subsequently the mixture is diluted with EtOAc and washed with

2N NaOH, H_2O brine, and finally dried over $MgSO_4$. Purification on silica gel yields the coupled product. ^1H NMR ($CDCl_3$, δ ppm) 7.55 (1H, d, J = 7 3 Hz), 7 42 (1H, s) 7 06 (1H, d, J = 1 1 Hz), 6 84 (1H, d, J = 7 5 Hz), 3 96-4 00 (1H, m) 3 91 (3H, s), 2 98-3 01 (1H, m), 2 39 (3H, d, J = 1 1 Hz), 2.25 (3H, s), 1 82 1 90 (4H, m), 1.31 (6H, d J = 7 0Hz), 0 80 (6H, t, J = 7.5 Hz)

Step B

The Suzuki product of step A (718mg) is dissolved in 3N HCl (50mL) and heated to 70 °C overnight. The reaction mixture is cooled to ambient temperature neutralized with 2N NaOH, and extracted with $CHCl_3$ (100mLx2) Drying over $MgSO_4$ yields the pyridone, which is used in step C without any further purification

Step C

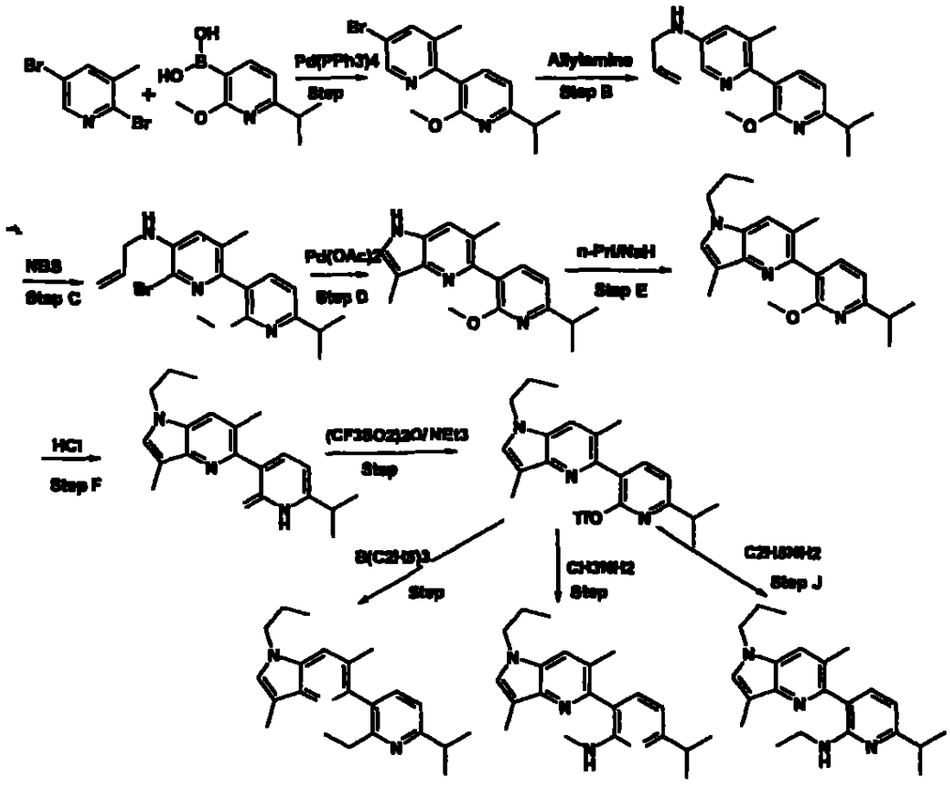
The pyridone (700mg) of step B is dissolved in CH_2Cl_2 Triethylamine (3 eq) is added, followed by dropwise addition of Tf_2O (1 5 equivalents) at 0 C After being stirred at rt for 2h, the reaction mixture is washed with H_2O brine and dried over $MgSO_4$ The triflate is used in step D without any further pur fication

Step D

The crude material of step C (48mg) $Pd(PPh_3)_4$ (11 5mg) and triethylborane (0.5mL, 1N in hexane) are dissol ed in toluene (2mL) After addition of 2N Na_2CO_3 (0 5mL), the mixture is degassed and then heated at 85 °C overnight The solution is diluted with EtOAc and washed with 2N NaOH, H_2O brine, and finally dried over $MgSO_4$. Purification on silica gel yields the title compound. ^1H NMR ($CDCl_3$ δ ppm) 7.46 (1H, d, J = 7 9 Hz) 7 44 (1H, s) 7 09 (1H, d, J = 0 8 Hz), 7 06 (1H, d, J = 7 7 Hz) 3 97-4 01 (1H m) 3 10-3 13 (1H, m) 2 60 (2H, q, J = 7 3Hz), 2 39 (3H, d, J = 0 8 Hz), 2 16 (3H, s) 1 81 1 90 (4H, m) 1 32 (6H, d, J = 7 0Hz), 1 15 (3H, t, J = 7.3Hz), 0 80 (6H, t, J = 7 6 Hz)

EXAMPLE 12

Synthesis of 5-(2-ethyl-6-isopropyl-pyridin-3-yl)-3,6-dimethyl-1 propyl-1H pyrrolo[3,2-b]pyridine, [3-(3,6-dimethyl-1 propyl-1H pyrrolo[3,2-b]pyridin-5-yl)-6-isopropyl-pyridin 2-yl]-methyl-amine and [3-(3,6-dimethyl-1 propyl-1H pyrrolo[3,2-b]pyridin-5-yl)-6-isopropyl-pyridin-2-yl]-ethyl-ami



Step A

A mixture of 2 5-dibromo-3 methylpyridine (5 02g, 0 02mol)), 2 methoxy-6-isopropyl 3 pyridylboronic acid (4 10g, 0.021mol), $Pd(PPh_3)_4$ (924mg) aqueous Na_2CO_3 solution (1 0M, 40ml), and toluene (50ml) is heated at 100 °C under the N2 atmosphere overnight The reaction mixture is cooled to room temperature and separated The aqueous layer is extracted with ethyl acetate The combined organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate g ves prod ct as clear oil LCMS m/z 323 3 (M+H)

Step B

A mixture of bromide (9 63g, 0 03mol) allylamine(6 75ml) BINAP(1.5g) $Pd_2(dba)_3$(1 0g), NaO-t Bu(5 77g) in toluene (150ml) is heated at 100 °C under N_2 atmosphere overnight. The reaction mixture is cooled to room temperature and quenched with water The resulting mixture is separated and extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate gives product as clear oil LCMS m/z 298.3 (M+H)

Step C

The starting material (6 67g) is taken in anhydrous $CHCl_3$(100ml) 1 0 equivalent of NBS is added in one portion at 0 °C The reaction is complete in 0 5 hour The reaction mixture is washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate g ves product as clear oil LCMS m/z 376 4 (M+H)

Step D

A mixture of bromide (6 6g), tetrabutylammon um bromide(7 07g), K_2CO_3(7.28g), $Pd(OAc)_2$(150mg) in DMF(70ml) is heated at 80 C under N2 atmosphere for 0 5 hour The reaction mixture is cooled to room temperature and diluted with water The resulting mixture is extracted with ethyl acetate The combine organic layers are washed with brine and dried w th Na_2SO_4 Purification by flash column with hexane/ethyl acetate gives product as off white solid LCMS m/z 296 4 (M+H)

Step E

NaH (100mg, 60% in mineral oil) is added to a solution of starting material (58mg) in anhydrous DMF (5ml) and stirred for 10minutes 1 iodopropane (0 5ml) is added and stirred for 05 hour The reaction mixture is carefully quenched with 1ml of methanol and diluted with water The resulting mixture is extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate gives product as clear oil LCMS m/z 338 4 (M+H)

Step F

Starting material (360mg) is taken into 4N HCl (20ml) and heated at 75 °C overnight. Reaction mixture is cooled to 0 C and the pH value is adjusted to ~12 by adding 10N aqueous NaOH solution The resulting mixture is extracted with chloroform The combine

organic layers are washed with brine and dried with Na_2SO_4 Concentration gives crude product as n off white sol d It is sed for the next step reaction w thout further purification LCMS m/z 324.4 (M+H)

Step G

Pyridone (330mg) is taken in anhydrous methylene chloride (20ml) and cooled to 0 C Triflic anhydride (1 5equiv) is added followed by the addition of triethylamine(2 equi) The reaction is complete in 0 5 hour The reaction mixture is washed with saturated NaHCO3 and dried with Na_2SO_4 The crude product s used for the next step reaction without further purification LCMS m/z 456 4 (M+H)

Step H

A mixture of triflate(180mg), LiCl(84mg), $Pd(PPh_3)_4$(23mg), Na_2CO_3(1 0M in water 1ml), $B(C_2H_5)_3$(1 0M in hexane, 1 5ml) in toluene(2ml) is heated at 100 °C in sealed tube for 2 hours. The resulting mixture s cooled to room temperature a d extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO Purification by flash col mn with hexane/ethyl acetate gives 5-(2-ethyl-6-isopropyl pyridin 3 yl)-3 6-dimethyl 1 propyl 1H pyrrolo[3,2 b]pyridine as clear oil LCMS m/z 336 4 (M+H)

Step I

Triflate (230mg) is taken in anhydrous *N*-methylpyrrolidinone (2ml) CH_3NH_2 is added as a solut on of NMP (~5 5M 2ml) The resulting mixture is heated at 85°C in a sealed tube o ern ght. The reaction m xture is cooled to room temperature and diluted with water The resulting mixture is extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate gi es [3 (3 6-dimethyl 1 propyl 1H-pyrrolo[3 2 b]pyridin-5 yl)-6-isopropyl-pyridin 2 yl]-methyl amine as clear oil LCMS m/z 337 4 (M+H)

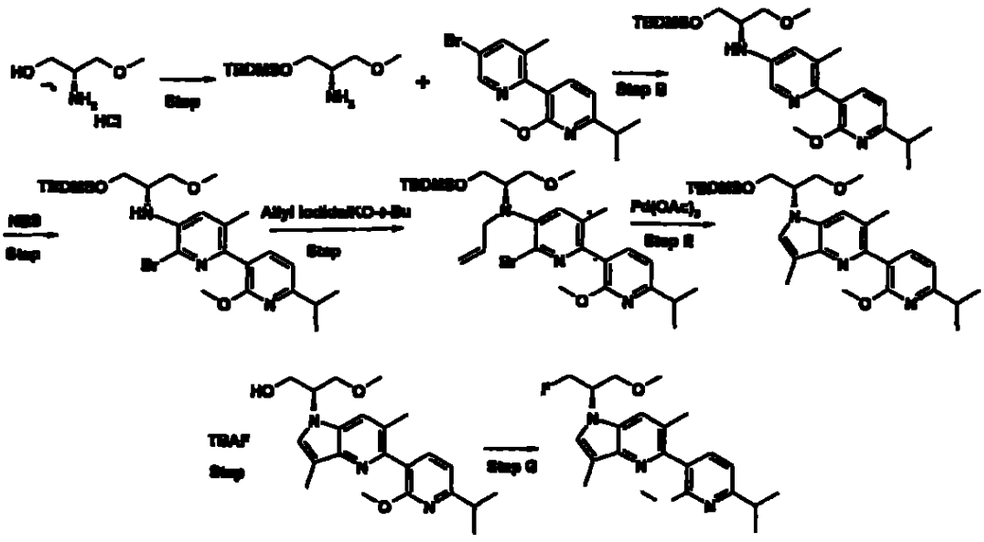
Step J

Triflate (420mg) is taken in anhydrous *N* methylpyrrolidinone (3ml), $C_2H_5NH_2$ is added as a solution of THF (2 0M 2ml) The resulting mixture is heated at 85 °C in a sealed tube overnight The reaction mixture is cooled to room temperature and diluted with water The resulting mixture is extracted with ethyl acetate. The combine organic layers are washed with

brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate gives [3 (3 6-dimethyl-1-propyl 1H-pyrrolo[3,2 b]pyridin-5 yl)-6-isopropyl-pyridin-2-yl]-ethyl-amine as clear oil LCMS m/z 351 5 (M+H)

EXAMPLE13

Synthesis of (R)-2 [5-(6-isopropyl-2-methoxy pyridin-3-yl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin-1 yl]-3-methoxy-propan-1-ol and 1-((S)-2-fluoro-1 methoxymethyl-ethyl)-5-(6-isopropyl-2-methoxy pyridin-3-yl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridine



Step A

(R)-2 Amino-3 methoxy-propan 1-ol hydrochloride (CAS# 148278-96-0) (6 74g) and imidazole(13.2g) are taken in anhydrous methylene chloride (300ml) TBDMSCl (21 9g) is added in one portion The reaction is carried on overnight. The reaction mixture is washed with water (200mlX3) and dried with Na_2SO_4 Concentration removes all volatiles. The crude product is used for next step reaction without further purification

Step B

A mixture of bromide (6.42g, 0 02mol) amine (1 5equiv), BINAP (1 0g), $Pd_2(dba)_3$(0 6g), NaO-*t* Bu(4 0g) in toluene(80ml) is heated at 85 °C under N_2 atmosphere overnight The reaction mixture is cooled to room temperature and quenched with water The resulting mixture is separated and extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO Purification by flash column with hexane/ethyl acetate gives product as clear oil Rf 0 3(Hexane/ethyl acetate 3/1)

Step C

The starting material (7 33g) is taken in anhydrous $CHCl_3$ (100ml) 1 0 equivalent of NBS is added in one portion at 0 °C The reaction is complete in 0 5 hour The reaction mixture is washed with brine and dried with Na_2SO_4 Purificat on by flash column with hexane/ethyl acetate gives product as clear oil Rf 0 3(Hexane/ethyl acetate 15/1)

Step D

Starting material (5 94g) is taken in nhydrous THF (100ml) Allyl iodide (3 6ml) is added followed by the addition of KO-t-Bu/THF solution (1 0M, 44ml) at room temperature The reaction is stirred at room temperature for 3 hours. The reaction mixture is quenched with water The result ng mixture is separated and extracted with ethyl acetate. The combine organic layers are washed with brine and dried with Na_2SO_4 The crude product is used for the next step reaction without further purification Rf 0 3(Hexane/ethyl acetate 19/1)

Step E

The crude product (6 4g) of previous reaction is taken in DMF (60ml) followed by the addition of tetrabutylammoni m bromide (4 45g) K_2CO_3 (4 58g), $Pd(OAc)_2$ (125mg) The resulting mixture is heated at 85 °C under N_2 atmosphere for one ho r The reaction mixture is cooled to room temperature and diluted with water The result g mixture s extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate gives product as clear oil 0 3(Hexane/ethyl acetate 5/1)

Step F

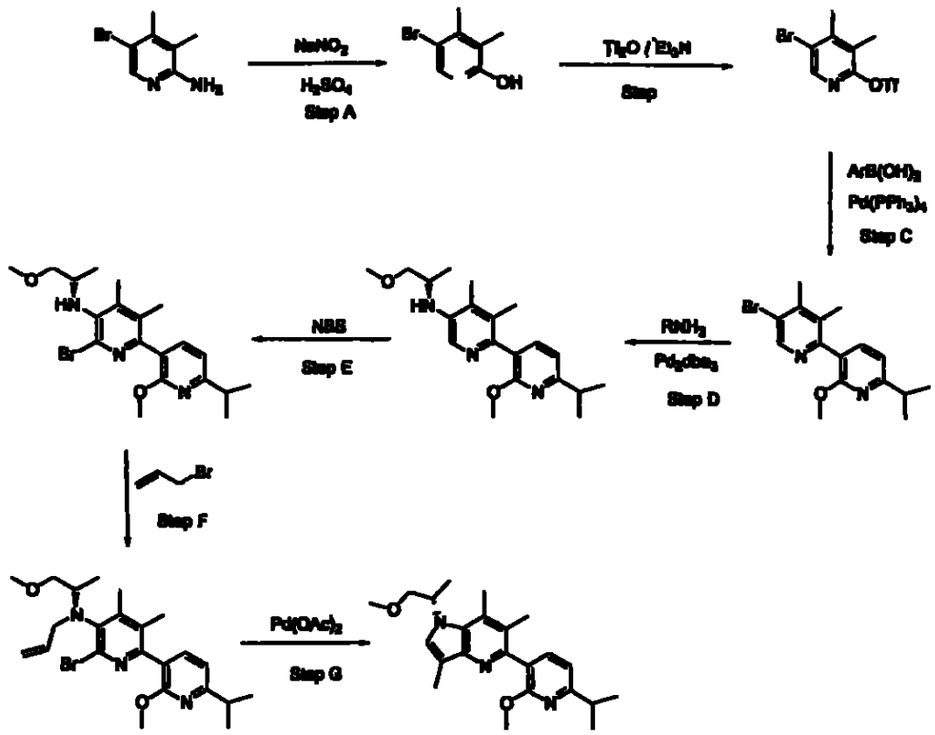
Starting material (5 43g) is taken n THF (60ml) followed by the addition of tetrabutylammonium fluoride (2 equi) at room temperature The reaction is complete after 2 hours The reaction mixture is washed with water brine and dried with Na_2SO Concentration gives (R)-2 [5-(6 isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] 3 methoxy propan 1-ol as an off white solid LCMS m/z 384 4 (M+H)

Step G

Starting material (1 15g, 3mmol) is taken in anhydrous methylene chloride (50ml) followed by the addition of [Bis(2 methoxyethyl)amino]sulfur trifluoride (2 equiv) at room temperature The reaction is stirred at room temperature overnight. The reaction mixture is carefully quenched with ice-water The resulting mixture is separated and extracted with methylene chloride and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate gives 1-((S)-2 fluoro-1 methoxymethyl-ethyl)-5-(6-isopropyl-2-methoxy pyridin 3 yl)-3 6-dimethyl-1H-pyrrolo[3,2-b]pyridine as clear oil 0 3(Hexane/ethyl acetate 5/1)

EXAMPLE 14

Synthesis of 5-(6-Isopropyl-2-methoxy-pyridin-3-yl)-1-((S)-2-methoxy 1 methyl-ethyl)-3,6,7 trimethyl-1H pyrrolo[3,2-b]pyridine



Step A

2 Amino-5-bromo-3 4-dimethylpyridine (201 mg) in H_2SO_4 (2 5N 2 4mL) is cooled to 0 C and subsequently treated dropwise with sodium nitrite (104mg) in H_2O (1 mL) The solid is collected and washed with H_2O and dried to afford 2 hydroxy 5 bromo-3 4-dimethylpyridine LCMS m/z 202.2 and 204.2 (M+H)

Step B

2 Hydroxy 5 bromo-3 4-dimethylpyridine (165 mg) is dissolved in $CHCl_3$ (3mL) Triflic anhydride (0 17 mL) and Et_3N (0 17mL) are added at r t and the mixture is stirred for 30 min The mixture s evaporated and dissolved in EtOAc/hexane (2 8) and washed with sat. $NaHCO_3$, H_2O and dried Evaporation affords the triflate LCMS m/z 334 0 and 336 0 (M+H)

Step C

The above triflate (272mg) and 2-methoxy-6-isopropyl 3 pyridineboronic acid are dissolved in DME (3 5mL) After 10m n of degassing, tetrakis(triphenylphosphine)palladium(0) (12mg) is added, followed by 1 min of degassing Upon addition of an aqueous 1N sodium carbonate solution (1 63mL) and LiCl (140mg), the reaction mixture is heated to 90 C for 16h Subsequently the crude mixture is put into water (100mL), extracted with EtOAc/hexane (20 80 3x20mL), and dried over sodium sulfate Purification on silica gel affords 3-(5 bromo-3 4-d methyl pyrid 2 yl)-2 methoxy-6-isopropylpyridine LCMS m/z 335 1 and 337 1 (M+H)

Step D

3-(5-bromo-3 4-dimethyl pyridin 2 yl)-2 methoxy-6-isopropylpyridine (85mg) (S)-2 methoxy-1-methyl-ethylamine (34mg), Pd_2dba_3 (12mg), BINAP (16mg) and t BuONa (37mg) are dissolved in toluene (3 5mL) The reaction mixture is heated to 90 C for 6h Subsequently the crude mixture is put into water (10mL) extracted with EtOAc/hexane (1 1 2x10mL), and dried over sodium sulfate Purification on silica gel affords 3 {5 [(S) 2 methoxy 1-methyl-ethylam no] 3 4-dimethyl pyridin 2 yl} 2 methoxy-6 isopropylpyridine LCMS m/z 344 4 (M+H)

Step E

3 {5 [(S)-2-methoxy-1 methyl-ethylamino] 3 4-dimethyl-pyrid n 2 yl} 2 methoxy-6-isopropylpyridine (42 mg) is dissolved in $CHCl_3$ (1mL) Upon addition of NBS (24mg), the reaction mixture is stirred at 25 C for 30 min Subsequently the crude mixture is put into water (10mL), extracted with EtOAc/hexane (1 4 2x5mL), and dried over sodium sulfate Purificat on on silica gel affords 3 {6 bromo-5-[(S) 2-methoxy-1 methyl-ethylamino]-3 4-

dimethyl pyridin-2 yl} 2-methoxy-6-isopropylpyridine LCMS m/z 422.3 and 424.3 (M+H)

Step F

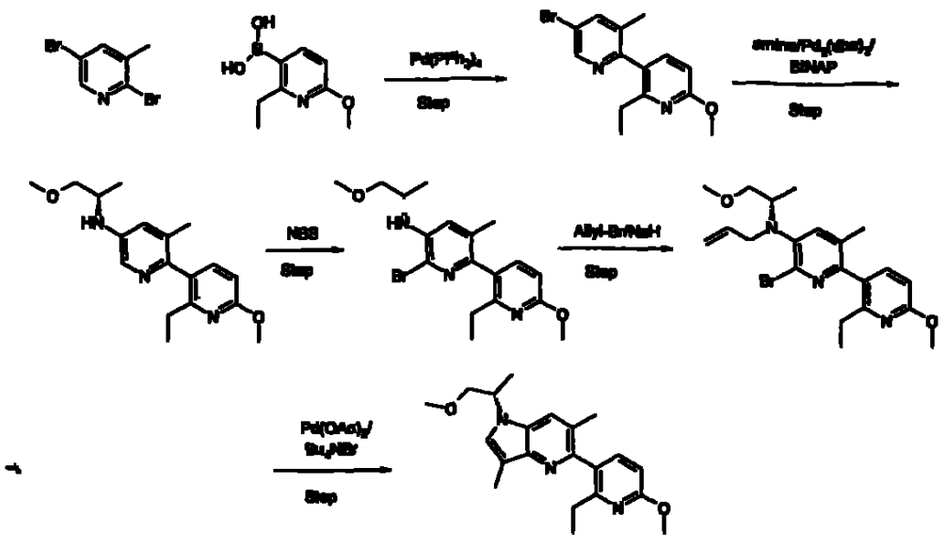
3 {6-bromo-5 [(S)-2-methoxy 1-methyl-ethylamino]-3 4-dimethyl-pyridin 2 yl} 2-methoxy 6-isopropylpyridine (2 0 g) is dissolved in NMP (15 ml) Upon addition of NaH (60%, 380mg), the reaction mixture is stirred at 25 °C for 30 min before allyl bromide (0 82 mL) is added The reaction mixture is then heated to 50 °C overnight. Subsequently the crude mixture is put into water (10mL), extracted with EtOAc/hexane (1·4 2x50mL), and dried over sodium sulfate Purification on silica gel affords 3-{6-bromo-5 [(S)-N-allyl 2 methoxy-1-methyl-ethylamino] 3 4-dimethyl-pyridin 2 yl} 2-methoxy-6-isopropylpyridine LCMS m/z 462.4 and 464.4 (M+H)

Step G

3 {6 bromo-5-[(S)-N-allyl 2-methoxy 1-methyl-ethylamino] 3 4-dimethyl pyridin 2 yl} 2 methoxy-6-isopropylpyridine (0 75g) is dissolved in DMF (6mL) After 10min of degassing, $Pd(OAc)_2$ (36mg) is added, followed by 1 min of degassing Upon add t on of potassium carbonate (670 mg) and Bn_4NBr (650mg) the reaction mixture is heated to 90 °C for 2h Subsequently the crude mixture is put into water (100mL), extracted with EtOAc/hexane (1 2 3x50mL) and dr ed over sod um sulfate Purification on silica gel affords 5-(6-Isopropyl 2-methoxy pyridin 3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-3 6 7 trimethyl 1H pyrrolo[3,2 b]pyridine LCMS m/z 382 3 (M+H)

EXAMPLE 15

Synthesis of 5-(2-ethyl-6-methoxy pyridin-3-yl)-1-((*S*)-2-methoxy 1 methyl-ethyl)-3, 6-dimethyl-1H pyrrolo[3,2-b]pyridine



Step A

2,5-dibromo-3-methylpyridine (18 90g) and the pre ously described 2-ethyl-6-methoxy 3 pyrid ne boron c acid (13 70g) are d ssolved in DME (200mL) After degass ng, tetrakis(triphenylphosphine)palladium (0) (3 60g) is added A second degassing is followed by addition of a 5N sodium carbonate solution (30mL) whereupon the reaction is heated to 80 °C for 16h The yellowish m xt re is then put nto wate (500mL), extracted with DCM (2x300mL), and dried over sod m sulfate Purificat on on silica gel affords the coupled product LCMS m/z 306 94 (M+H)

Step B

The purified compound (6 40g) of step A and (*S*)-1-methoxy 2-aminopropane (2 04g) are dissolved in toluene (80mL) and briefly degassed Subsequently $Pd_2(dba)_3$ (1 03g), *rac*-2,2 b s(diphenylphosphino) 1 1 -binaphthyl (0 76g) and sodium *tert* butoxide (2 81g) are added before the mixture s heated to 70 °C for 16h The black solution is then put into water (400mL) and sat. sodium bicarbonate (100mL), extracted with DCM (3x300mL) and dried over magnesium sulfate Flushing the crude material through a plug of silica gel affords the 5-aminopyridine as a semi-crude that is used in step C LCMS m/z 316 35 (M+H)

Step C

The amino compound of step B is dissolved in chloroform (200mL) and NBS (0 9-1 0 eq) is added in portions until TCL control verifies full conversion of the starting material

Subsequently the yellowish mixture is put into water (200mL), extracted with DCM (3x100mL) and dried over magnesium sulfate Purification on silica gel affords the bromide LCMS m/z 394.21 (M+H)

Step D

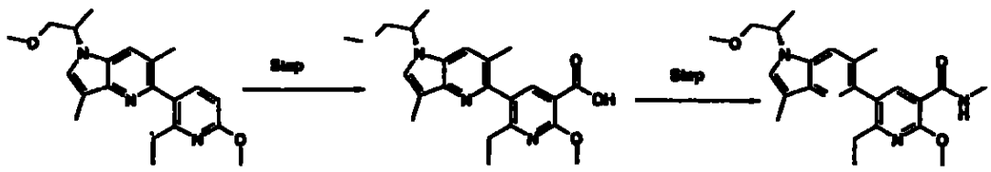
The purified bromide (7 59g) of step C and allyl bromide (2 04mL) are dissolved in DMF (100mL) Sodium hydride (1 16g) is added in 3 portions and the reaction is stirred for 90 min at rt After TLC control confirms some starting material is still remaining, 0.25 equivalents of both reagents are added to drive the reaction to completion The mixture is then put into water (500mL) and extracted with ethyl ether (2x300mL) The combined organic layers are washed with water (100mL) dried over magnesium sulfate and purified on silica gel to afford the allylated amine LCMS m/z 434.23 (M+H)

Step E

The allyl compound (7 89g) of step D tetrabutylammonium bromide (5 85g) palladium acetate (0 41g), and potassium carbonate (7 53g) are dissolved in DMF (150mL) After heating to 80 °C for 30 min the mixture is worked-up according to step D Final purification on silica gel affords the title compound LCMS m/z 354 39 (M+H)

EXAMPLE 16

Synthesis of 6-ethyl-2 methoxy 5-[1-((*S*)-2-methoxy 1 methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridin-5-yl]-*N* methyl-nicotinamide



Step A

5-(2 Ethyl-6-methoxy-pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine (135mg) is dissolved in THF (10mL) and then cooled to -40 °C Upon addition of *t* BuL (0 45mL, 1 7N in pentane) the temperature is elevated to 0 °C and kept there for 30 min Prior to injecting gaseous carbon dioxide, the temperature is brought to 78 °C After injection the solution is kept at this temperature for another 10 min and is then put into 1N NaOH (100mL) After washing the solution with ethyl ether (2x100mL), the aqueous

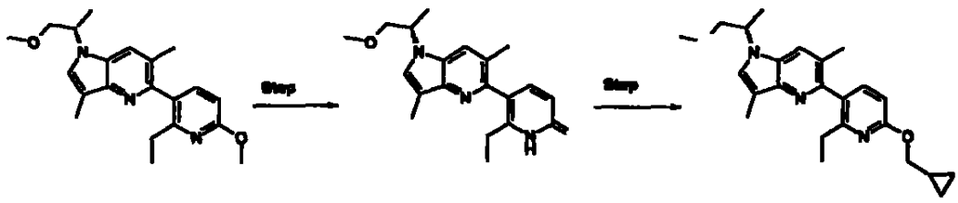
l yer s neutral zed and extracted with DCM (3x100mL) The combined DCM phases are dried over magnesium sulfate The crude has suffic ent purity and is used in step B without any further purification LCMS m/z 398 41 (M+H)

Step B

The crude mixture (50mg) of step A, BOP (84mg), and Huenig base (67µL) are dissolved in THF (5mL) The mixture is stirred for 5 min before methylamine (250µL, 2N in THF) is added After stirring for 16h, the yellowish solution is put into water (100mL), extracted with DCM (3x100mL) and dried over magnesium sulfate Final purification on silica gel affords the title compound LCMS m/z 411 41 (M+H)

EXAMPLE 17

Synthesis of 5-(6-cyclopropylmethoxy 2-ethyl-pyridin-3-yl)-1-((*S*)-2-methoxy 1 methyl-ethyl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridi e



Step A

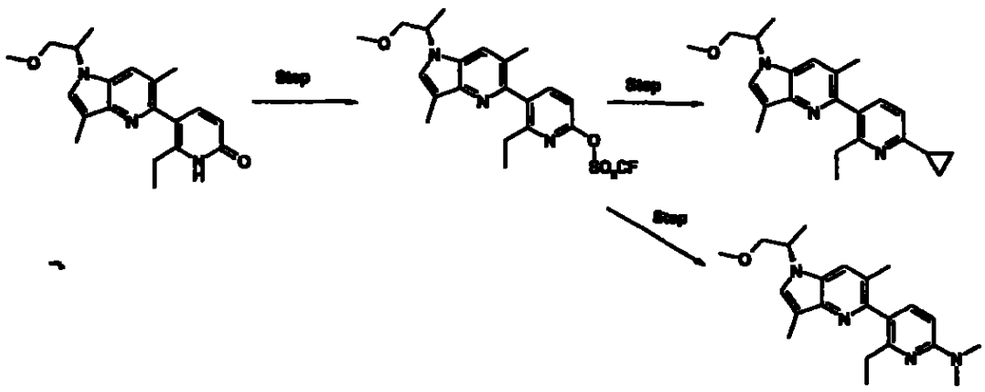
5-(2 Ethyl-6-methoxy-pyrid n-3-yl)-1-((S)-2-methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridine (5 00g) is dissolved in 4N HCl (150mL) and heated to 75 °C for 7 days Once TLC control verifies mostly hydrolyzed material 10N NaOH (60 0mL) and sat sodium bicarbonate (200mL) are added Extraction with DCM (3x200mL), drying over magnesium sulfate and purification on silica gel affords the pyridone LCMS m/z 340 06 (M+H)

Step B

The pyridone (50mg) of step C bromomethylcyclopropane (500mg), and potassium carbonate (500mg) are dissolved in DMF (3 0mL) After being stirred over night at rt, the mixture is put into water (100mL), extracted with DCM (3x100mL), and dried over magnesium sulfate Purification on silica gel affords the title compound LCMS m/z 394 16 (M+H)

EXAMPLE 18

Synthesis of 5-(6-cyclopropyl-2-ethyl-pyridin-3-yl)-1-((*S*)-2-methoxy 1 methyl-ethyl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridine and {6-ethyl-5-[1-((*S*)-2-methoxy-1 methyl-ethyl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridin-5-yl] pyridin 2-yl}-dimethyl-amı e



Step A

6-Ethyl 5 [1-((S)-2-methoxy 1 methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridin 5 yl] 1H-pyridin-2-one (2 00g) and triethylamine (2 05mL) are dissolved in DCM (100mL) After being cooled to 0 °C trifluoromethanesulfonic anhydride is added and the reaction is stirred for 30 min at that temperature Subsequently the yellowish mixture is put into water (200mL), extracted with DCM (3x200mL) and dried over magnesium sulfate Purification on silica gel affords the triflate LCMS m/z 472.26 (M+H)

Step B

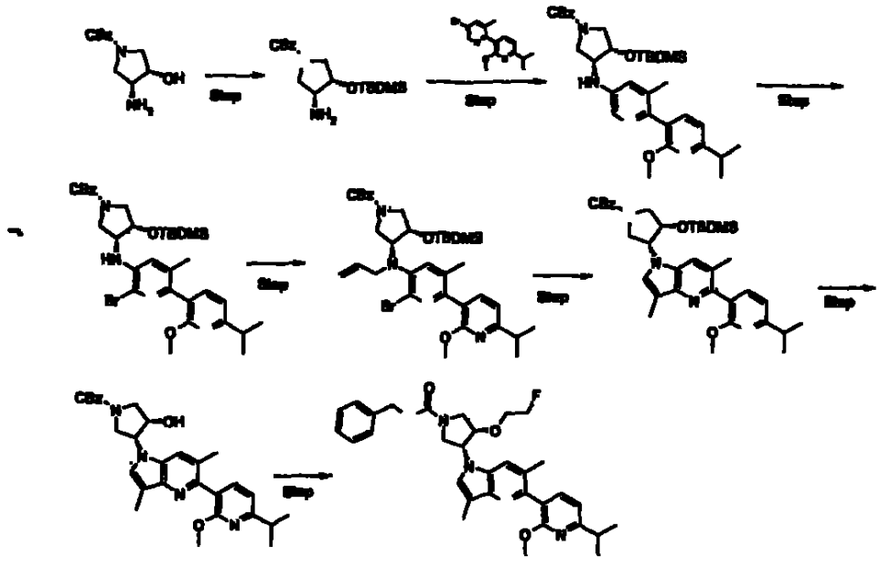
The triflate (50mg) of step A and cyclopropyl boronic acid (91mg) are dissolved in toluene (5mL) After being degassed for 5 min, tetrakis(triphenylphosphine)palladium (0) (12mg) is added and the mixture is degassed again. Adding a potassium carbonate solution (0 50mL, 2N) is followed by heating to 110 °C for 16h Subsequently the mixture is put into water (100mL), extracted with DCM (3x100mL) and dried over magnes ium sulfate Purification on silica gel affords the title compound. LCMS m/z 364.45 (M+H)

Step C

The triflate (100mg) of step A is dissolved in a 5N NMP solution of dimethylamine (1 50mL) and subsequently heated to 80 °C for 8h The reaction mixture is then put into water (100mL), extracted with DCM (3x100mL), and dried over magnesium sulfate Purification on silica gel affords the title compound. LCMS m/z 367.43 (M+H)

EXAMPLE 19

Synthesis of (3S,4R)-3-(2-fluoro-ethoxy)-4-[5-(6-isopropyl-2-methoxy pyridin-3-yl)-3,6-dimethyl-pyrrolo[3,2-b]pyrid n-1 yl]-pyrrolid ne-1-carboxylic acid benzyl ester



Step A

To a solution of (3R,4S)-3-amino-4-hydroxy-pyrrol dine-1-carboxylic acid benzyl ester (3 g) in DCM (15 mL) is added imidazole (1.3 g) at 0 C tert Butyldimethylsilyl chloride (1 9 g) is added to the above solution at 0°C After stirring at 0 °C for 30 min, the ice-bath is removed The mixture is stirred at RT for 2h and is poured into EtOAc (200 mL) The mixture is washed with water and brine, and is dried over $MgSO_4$ After removal of the solvent, the residue is purified by flash column chromatography to give (3R,4S) 3-amino-4-(tert butyl dimethyl silanyloxy)-pyrrolidme-1-carboxylic acid benzyl ester as colerless oil LCMS Rt 1 40 min, m/z 351 07 (M+H)

Step B

To a solution of (3R 4S)-3-amino-4-(tert butyl-dimethyl-s lanyloxy)-pyrrolidme-1-carboxylic acid benzyl ester (3 g) and 5-bromo-6 isopropyl-2 -methoxy 3-methyl [2 3']bipyridinyl (3 02 g) in toluene (20 mL) is added $Pd_2(dba)_3$ (0 313 g) BINAP (0 43 g) and NaOtBu (1 15 g) at RT The mixture is stirred at 80 °C for 22 h and is poured into water (150 mL) The mixture is extracted with EtOAc and the combined extracts are washed with brine After drying over

$MgSO_4$, the solvent is removed under reduced pressure The residue is purified by flash column chromatography on s lica gel to afford (3S 4R)-3-(tert butyl-dimethyl-silanyloxy)-4-(6 isopropyl 2 -methoxy 3-methyl [2,3']bipyridinyl 5 ylamino)-pyrrolidine-1-carboxylic acid benzyl ester as amorphous LCMS Rt 1.62 min, m/z 591 15 (M+H)

Step C

To a stirred solution of (3S 4R)-3-(tert butyl-dimethyl-silanyloxy)-4-(6 isopropyl 2 methoxy 3 methyl-[2 3']bipyridinyl 5-ylamino)-pyrrolidine-1-carboxylic acid benzyl ester (4 07 g) in chloroform (25 mL) is added NBS (1.23 g) at RT After stirring at RT for 15 min, the solvent is evaporated under reduced pressure and the residue is purified by flash column chromatography on silica gel to give (3R,4S)-3-(6-bromo-6 isopropyl 2 methoxy 3 methyl-[2,3']b pyridinyl-5 ylamino)-4-(tert butyl-dimethyl-silanyloxy)-pyrrolidine 1-carboxylic acid benzyl ester as colorless amorphous Rf (hexane EtOAc = 2 1) = 0 55

Step D

To a stirred solution of (3R,4S)-3-(6-bromo-6 isopropyl-2 methoxy 3-methyl [2 3']bipyridinyl 5 ylamino)-4-(tert-b tyl-dimethyl silanyloxy)-pyrrol dine 1-carboxylic acid benzyl ester (4 03 g) in THF (25 mL) is added solution of KOtB in THF (2 41 mL, 1 M) at RT Allyl bromide (2 04 mL) is added to the above solution over 10 min at RT The mixture is stirred at RT for 16 h and is poured in to water The mixture is extracted with EtOAc The combined extracts are washed with brine and are dried over $MgSO_4$. After removal of the solvent under reduced pressure the residue is purified by column chromatography on silica gel to give (3R,4S)-3-[allyl-(6-bromo-6 isopropyl-2 -methoxy-3 methyl [2 3']bipyridinyl 5 yl)-amino]-4-(tert-butyl-dimethyl-silanyloxy)-pyrrolidine-1 carboxylic acid benzyl ester as amorphous LCMS Rt 1 93 min, m/z 709 / 711 (M+H)

Step E

To a solution of (3R,4S) 3 [allyl-(6-bromo-6 isopropyl 2 methoxy 3 methyl [2,3']bipyridinyl 5 yl)-amino]-4-(tert butyl-dimethyl-silanyloxy)-pyrrolidine 1-carboxylic acid benzyl ester (3.2 g) in DMF (20 mL) is added $Pd(OAc)_2$ (81 mg), K_2CO_3 (1 87 g) and tetrabutylammonium bromide (1 6 g) at RT The mixture is stirred at 80 °C for 2 h and is poured into water The mixture is extracted with EtOAc. The combined extracts are washed

with brine and are dried over $MgSO_4$ After evaporation of the solvent under reduced pressure, the residue is purified by flash column chromatography on silica gel to give (3S 4R)-3-(tert butyl-dimethyl silanyloxy)-4 [5-(6-isopropyl 2-methoxy pyridin-3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl] pyrrolidine-1 carboxylic acid benzyl ester as amorphous LCMS Rt 1 62 min m/z 629 18 (M+H)

Step F

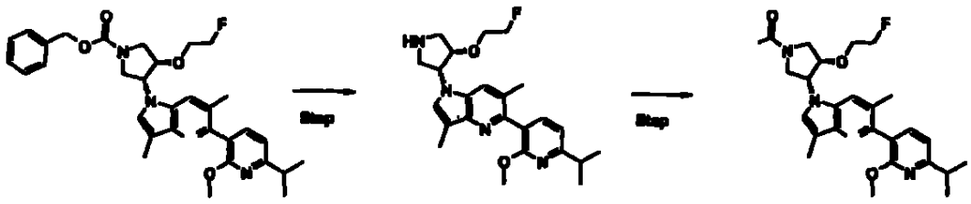
To a stirred solution of (3S 4R)-3-(tert butyl-dimethyl-silanyloxy)-4-[5-(6-isopropyl-2 methoxy-pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin 1 yl]-pyrrol dine-1 carboxylic acid benzyl ester (2 3 g) in THF (14 mL) is added a solution of tetrabutylammonium fluorid in THF (4 8 mL, 1M) at RT The mixture is stirred at RT for 10 min and is poured into ice-water (80 mL) The mixture is extracted with EtOAc. The combined extracts are washed with brine and are dried over Mg SO_4 After removal of the solvent under reduced press re, the residue is purified by flash column chromatography on silica gel to give (3S 4R) 3 hydroxy-4 [5-(6- sopropyl 2 methoxy-pyrid n-3 yl)-3 6 d methyl-pyrrolo[3 2-b]pyridin 1 yl] pyrrolidine 1-carboxylic acid benzyl ester as colorless amorphous LCMS Rt 1 45 min m/z 515 10 (M+H)

Step G

To a solution of (3S 4R)-3 hydroxy-4 [5-(6-isopropyl-2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl] pyrrolidine 1-carboxylic acid benzyl ester (1 88 g) in DMF (15 mL) is added sodi m hydride (0 44 g) and bromofluoroethane (0 82 mL) at RT After stirring at RT for 2 5 h, the mixture s poured into ice-water and is extracted with EtOAc The combined extracts are washed with brine and are dried over $MgSO_4$ After evaporation of the solvent under the reduced pressure, the residue is purified by flash column chromatography on silica gel to afford (3S 4R)-3-(2 fluoro-ethoxy)-4-[5-(6-isopropyl 2-methoxy-pyrid n-3 yl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] pyrrolidine-1-carboxylic acid benzyl ester as colorless amorphous LCMS Rt 1 49 min, m/z 561 11(M+H)

EXAMPLE 20

Synthesis of (3S,4R)-3-(2-fluoro-ethoxy)-4-[5-(6-isopropyl-2-methoxy pyridin-3-yl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin-1 yl] pyrrolidine-1-carboxylic acid methyl ester



Step A

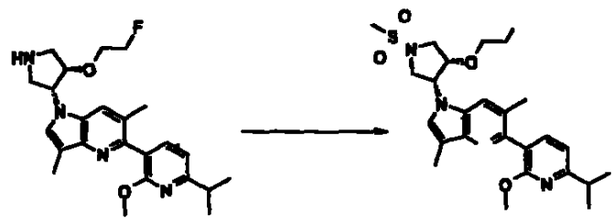
To a solution of (3S 4R)-3-(2 fluoro-ethoxy)-4-[5-(6-isopropyl-2 methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin-1 yl]-pyrrolidine-1-carboxylic acid benzyl ester (1 9 g) in EtOH (10 mL) is added 10 % Pd/C (0.3 g) at RT The suspension is stirred at RT under hydrogen for 14 h. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure The residue is purified by flash column chromatography on silica gel to give 1 [(3R,4S)-4-(2 fluoro-ethoxy)-pyrrolidin-3 yl] 5-(6-isopropyl-2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine as colorless amorphous. LCMS Rt 1.29 min, m/z 427 11 (M+H)

Step B

To a stirred solution of 1 [(3R,4S)-4-(2 fluoro-ethoxy)-pyrrolidin 3 yl] 5-(6-isopropyl 2 methoxy pyrid n 3 yl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridine (0 1 g) in DCM (1 mL) is added methyl chloroformate (0 03 mL) at RT After stirring at RT for 15 min, the reaction is quenched with aqueous saturated Na_2CO_3 (3 mL) The mixture is extracted with EtOAc The comb ned extracts are dried over $MgSO_4$ and are concentrated under reduced pressure The residue is purified by preparative TLC to give (3S,4R)-3-(2 fluoro-ethoxy)-4-[5-(6-isopropyl 2 methoxy pyridin-3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin
1 yl] pyrrolidine 1-carboxylic acid methyl ester as colorless amorphous LCMS Rt 1 39 min, m/z 485 13 (M+H)

EXAMPLE 21

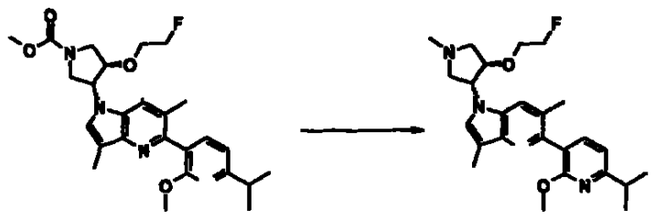
Synthesis of 1-[(3R,4S)-4-(2-fluoro-ethoxy)-1 methanesulfonyl-pyrrolid -3-yl]-5-(6-isopropyl-2-methoxy-pyridin-3-yl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridi



To a stirred solution of 1 [(3R,4S)-4-(2 fluoro-ethoxy)-pyrrolidin 3 yl] 5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine (0 1 g) in DCM (1 mL) is added methanesulfonyl chloride (0 03 mL) at RT After stirring at RT for 15 min, the reaction is q enched with aqueous saturated Na_2CO_3 (3 mL) The mixture is extracted with EtOAc The combined extracts are dried over $MgSO_4$ and are concentrated under reduced pressure The res due is purified by preparative TLC to give 1 [(3R,4S)-4-(2 fluoro-ethoxy)-1 meth nesulfonyl-pyrrol d n 3 yl] 5-(6-isopropyl-2-methoxy pyridin 3 yl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine as colorless amorphous LCMS Rt 1.35 min, m/z 505 10 (M+H)

EXAMPLE 22

Synthesis of 1 [(3R,4S)-4-(2 fl oro-ethoxy)-1 methyl-pyrrolidin-3-yl]-5-(6-isopropyl-2 methoxy pyridin-3-yl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

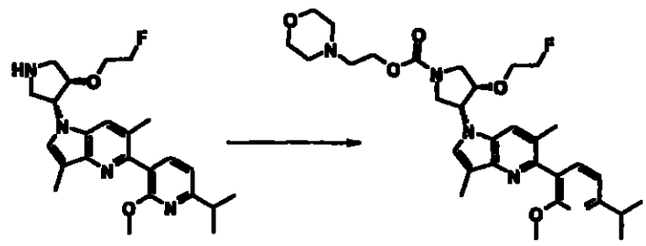


To a solution of (3S,4R)-3-(2 fluoro-ethoxy)-4 [5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl] pyrrolidine-1-carboxylic acid methyl ester (77 mg) in THF (1 mL) is added a solution of $LiAlH_4$ in THF (1 5 mL, 1 M) at RT After stirring at RT for 2 h the reaction is quenched with water The inorganic salts are removed by Celite filtration The filtrates are concentrated under reduced pressure and the residue is purified by flash chromatography on silica gel to afford 1 [(3R,4S)-4-(2-fluoro-ethoxy)-1-methyl-

pyrrolidin 3 yl] 5-(6-isopropyl-2-methoxy-pyridin-3 yl)-3 6-dimethyl-1H-pyrrolo[3,2 b]pyridine as colorless amorphous. LCMS Rt 1.24 min, m/z 441 14 (M+H)

EXAMPLE 23

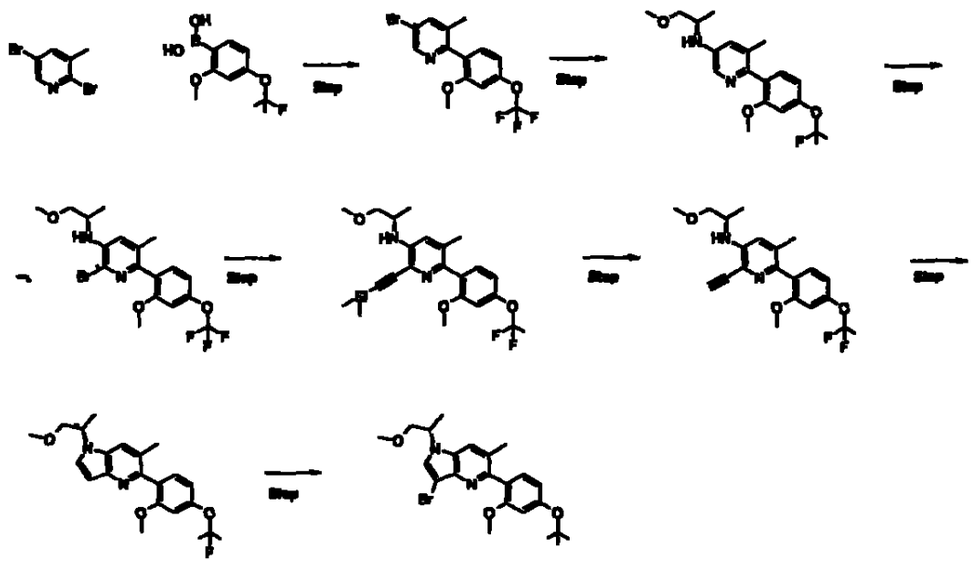
Synthesis of (3S,4R)-3-(2-fluoro-ethoxy)-4-[5-(6-isopropyl-2-methoxy-pyridin-3-yl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin-1-yl]-pyrrolidine-1-carboxylic acid 2-morpholin-4-yl-ethyl ester



To a stirred solution of 4-(2-hyroxyethyl)morpholine (0 063 mL) in DCM (1 mL) is 1 1 carbonyldiimidazole (84 mg) at RT After stirring at RT for 30 min, 1 [(3R,4S)-4-(2 fluoro-ethoxy)-pyrrolidin 3-yl]-5-(6-isopropyl 2-methoxy-pyridin 3 yl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine (0.2 g) s added to the mixture After stirring at RT for 1 day the mixture is purified by preparative HPLC to give (3S 4R)-3-(2 fluoro-ethoxy)-4-[5-(6-isopropyl 2 methoxy-pyridin-3 yl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin 1 yl] pyrrolidine-1 carboxylic acid 2-morpholin-4-yl-ethyl ester as amorphous LCMS Rt 1 38 min, m/z 584 (M+H)

EXAMPLE 24

Synthesis of 1-((S)-2-methoxy 1 methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-6-methyl-1H pyrrolo[3,2-b]pyridi e and 3-bromo-1-((S)-2-methoxy-1 methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-6-methyl-1H pyrrolo[3,2-b]pyridine



Step A

To a solution of 2 5-dibromo-3-methyl-pyridine (40 g) and 2-methoxy-4-trifluoromethoxy phenyl boronic acid (39 5 g) in tolue e (200 mL) is added $Pd(Ph_3P)_4$ (5 5 g) and 2M aqueous K_2CO_3 solution (160 mL) at RT The mixture is stirred at 85 °C for 16 h The mixture is poured into water and is extracted with EtOAc The combined extracts are washed with brine and are dried over Mg SO_4 After evaporation of the solvent the res due is purified by flash column chromatography on silica gel to give 5-bromo-2-(2-methoxy-4-trifluoromethoxy phenyl)-3 methyl pyridine as white solid MS 362 / 364 (M+H)

Step B

To a solution of give 5 bromo-2-(2 methoxy-4-trifluoromethoxy-phenyl)-3-methyl pyridine (1 04 g) in toluene (20 mL) is added (S)-2 methoxy-1 methyl-ethylamine (0 28 g), $Pd_2(dba)_3$ (0 11 g), BINAP (0 14 g) and NaOtBu (0 39 g) The mixture s stirred at 80 °C for 15h The mixture is poured into wate and is extracted with EtOAc The combined extracts are washed with brine and dried over $MgSO_4$ After removal of the solvent under reduced pressure the residue is purified by flash column chromatography on silica gel to give ((S)-2 methoxy-1

methyl-ethyl)-[6-(2 methoxy-4-trifluoromethoxy-phenyl)-5-methyl-pyridin-3 yl]-amine as amorphous Rf (hexane EtOAc = 2 1) = 0.3

Step C

To a solution of ((S)-2-methoxy-1-methyl-ethyl)-[6-(2-methoxy-4-trifluoromethoxy-phenyl)-5 methyl pyridin-3 yl]-amine (1 g) in chloroform (5 mL) is added NBS (0 48 g) at RT After stirring at RT for 5 min, the mixture is directly purified by flash column chromatography on silica gel to give [2-bromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-5 methyl-pyridin-3 yl]-((S)-2-methoxy 1-methyl-ethyl)-amine as white solid

Rf (hexane EtOAc = 4 1) = 0.3

Step D

To a solution of [2 bromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-5-methyl-pyridin 3-yl]-((S)-2 methoxy 1-methyl-ethyl)-amine (0.2 g) in DMF (1 mL) is added ethynyl trimethyl-silane (0 08 mL), Et_3N (0 09 mL) $PdCl_2(Ph_3P)_2$ (6 mg) and CuI (1 mg) at RT The mixture is stirred at RT for 14 h The mixture is poured into water and is extracted with EtOAc The combined extracts are washed with brine and are dried over $MgSO_4$ After evaporation of the solvent, the residue is purified by flash column chromatography on silica gel to give ((S)-2-bethoxy 1-methyl-ethyl)-[6-(2 methoxy-4-trifluoromethoxy phenyl)-5 methyl 2-trimethylsilanylethynyl-pyridin 3 yl]-amine as colorless oil. LCMS Rt 1 74 min m/z 467 15 (M+H)

Step E

To a solution of ((S)-2-bethoxy 1-methyl-ethyl)-[6-(2-methoxy-4-trifluoromethoxy phenyl)-5 methyl 2-trimethylsilanylethynyl-pyridin 3 yl]-amine (0 18 g) in THF (2 mL) is added a solution of nBu_4NF in THF (0 48 mL, 1 M) at RT After stirring at RT for 15 min, EtOAc is added to the mixture The sol tion is washed with water and brine and is dried over $MgSO_4$ After removal of the solvent under reduced pressure, the residue is purified by flash column chromatography on silica gel to give [2-ethynyl-6-(2 methoxy-4-tr fluoromethoxy-phenyl)-5 methyl-pyridin 3 yl]-((S) 2-methoxy 1 methyl-ethyl)-amine as colorless oil LCMS Rt 1 58 min, m/z 395 09 (M+H)

Step F

To a sol t on of give [2-ethynyl-6-(2 methoxy-4 trifluoromethoxy-phenyl)-5-methyl-pyridin-3 yl]-((S)-2 methoxy 1 methyl-ethyl)-amine (0 1 g) i NMP (3 mL) is added tBuOK (28 mg) at RT The mixture is stirred at 80 °C for 1h The mixture is diluted with EtOAc and is washed with water and brine After drying over $MgSO_4$, the solvent is evaporated The residue is purified by flash column chromatography on silica gel to give 1-((S)-2 methoxy 1 methyl-ethyl)-5-(2-methoxy-4 trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3 2 b]pyridine as amorphous. LCMS 1 30 min, m/z 395 05 (M+H)

Step G

To a solution of 1-((S)-2 methoxy 1-methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy-phenyl)-6-methyl 1H pyrrolo[3,2 b]pyridine (65 mg) in chloroform (2 mL) is added NBS (32 mg) The mixture is stirred t RT for 30 min and is diluted with EtOAc The mixture s washed with water and brin and dried ove $MgSO_4$ After removal of the solvent under reduced pressure, the residue is purified by preparative TLC to give 3 bromo-1-((S)-2 methoxy-1-methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6 methyl-1H pyrrolo[3,2 b]pyridine as white solid LCMS Rt 1 54 mi m/z 472 96 / 474 96 (M+H)

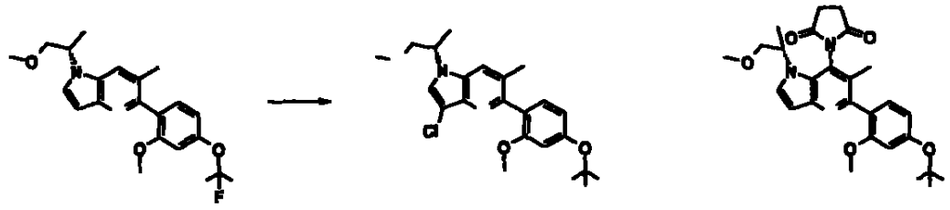
By using steps A F of Example 24 the follow ng compounds are prepared analogously

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-((S)-2 methoxy-1 methyl-ethyl)-6-methyl-1H pyrrolo[3 2 b]pyridine (LCMS Rt 1 40 min m/z 354 15 $(M+H)^+$)

(R)-2 [5-(6-Isopropyl 2 methoxy pyrid n 3 yl)-6-methyl pyrrolo[3,2 b]pyridin 1 yl]-butan 1-ol (LCMS Rt 1 39 min, m/z 354 12 $(M+H)^+$)

EXAMPLE 25

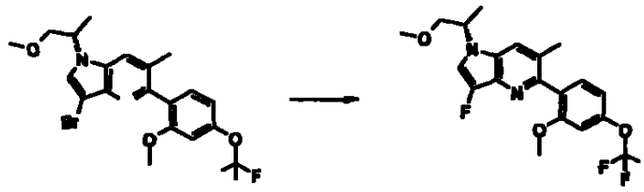
Synthesis of 3-chloro-1-((S)-2-methoxy 1 methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl-1H pyrrolo[3,2-b]pyridin and 1 [1-((S)-2-methoxy 1-methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-6-methyl-1H pyrrolo[3,2-b]pyridin 7 yl] pyrrolidine-2,5-dione



To a solution of 1-((S)-2 methoxy-1 methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H-pyrrolo[3 2-b]pyridine (40 mg) in chloroform (1 mL) is added NCS (15 mg) at RT After stirring at RT for 15 h the mixture is directly purified by preparative TLC to give 3-chloro-1-((S)-2-methoxy 1 methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H-pyrrolo[3 2 b]pyridine (white solid, LCMS 1 53 min, m/z 429 02 / 431 02 $(M+H)^+$) and 1-[1-((S)-2 methoxy-1-methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy-phenyl)-6-methyl 1H-pyrrolo[3,2-b]pyridin 7 yl]-pyrrolidine-2 5-dione (amorphous, LCMS Rt 1 38 min, m/z 492 09 $(M+H)^+$)

EXAMPLE 26

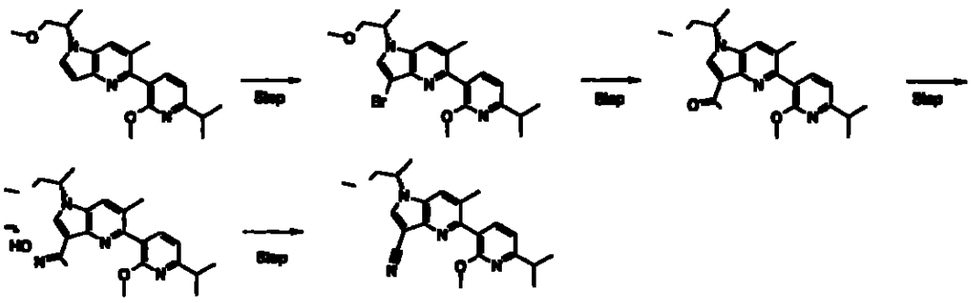
Synthesis of 3-fluoro-1-((S)-2-methoxy 1 methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-6-methyl-1H pyrrolo[3,2-b]pyridine



To a stirred solution of 3 bromo-1-((S)-2-methoxy 1-methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy-phenyl)-6-methyl 1H pyrrolo[3,2-b]pyridine (17 mg) in THF (1 mL) is added a solution of t-BuLi in pentane (0 09 mL, 1 7 M) at 78 °C After stirring at the same temperature for 1 h, a solution of N fluorobenzene-sulfonimide (46 mg) in THF (1 mL) is added. The mixture is stirred at 78 °C for 30 min and at 0 °C for 30mim The mixture is poured into water and is extracted with EtOAc The combined extracts are dried over $MgSO_4$ and are concentrated under reduced pressure The residue is purified by preparative TLC to give 3 fluoro-1-((S)-2 methoxy-1 methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy-phenyl)-6-methyl 1H pyrrolo[3,2 b]pyridine as amorphous LCMS Rt 1 49 min, m/z 413 02 (M+H)

EXAMPLE 27

Synthesis of 3-bromo-5-(6-isopropyl-2-methoxy pyridi -3-yl)-1-((S)-2-methoxy-1 methyl-ethyl)-6-methyl-1H pyrrolo[3,2 b]pyridine and 5-(6-isopropyl-2 methoxy-pyrid n-3-yl)-1-((S)-2-methoxy 1 methyl-ethyl)-6-methyl 1H pyrrolo[3,2-b]pyridine-3-carbonitrile



Step A

To a solution of 5-(6-isopropyl 2 methoxy-pyridin-3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-6-methyl 1H-pyrrolo[3 2-b]pyr d ne (1 25 g) n chloroform (10 mL) is added NBS (0 66 g) at 0 °C The mixture is stirred at RT for 2 h and is diluted with DCM The mixture is washed with water and brine After drying over $MgSO_4$, the solvent is removed under reduced pressure The residue is purified by flash column chromatography on sil ca gel to give 3 bromo-5-(6-isopropyl 2 methoxy-pyridin 3 yl)-1-((S)-2-methoxy 1 methyl-ethyl)-6-methyl-1H pyrrolo[3 2-b]pyrid ne as white crystal LCMS Rt 1.59 min, m/z 432 / 434 (M+H)

Step B

To a solution of 3-bromo-5-(6 isopropyl 2 methoxy-pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-6-methyl 1H pyrrolo[3 2-b]pyridine (4 g) n THF (4 mL) is treated with n BuLi in hexane (0 44 mL, 1 6 M) at 70 °C After stirring at 70 °C for 40 min DMF (0 11 mL) is added to the mixture The mixture s st rred at 70 °C for 90 min The reaction is quenched with water and the mixture is extracted with EtOAc The extract is dried over MgSO and is concentrated under reduced pressure The residue is purified by preparative TLC to give 5-(6-isopropyl 2 methoxy-pyridin 3 yl)-1-((S)-2 methoxy-1 methyl-ethyl)-6-methyl 1H pyrrolo[3,2-b]pyridine-3-carbaldehyde as colorless amorphous LCMS Rt 1 50 min m/z 382.20 (M+H)

Step C

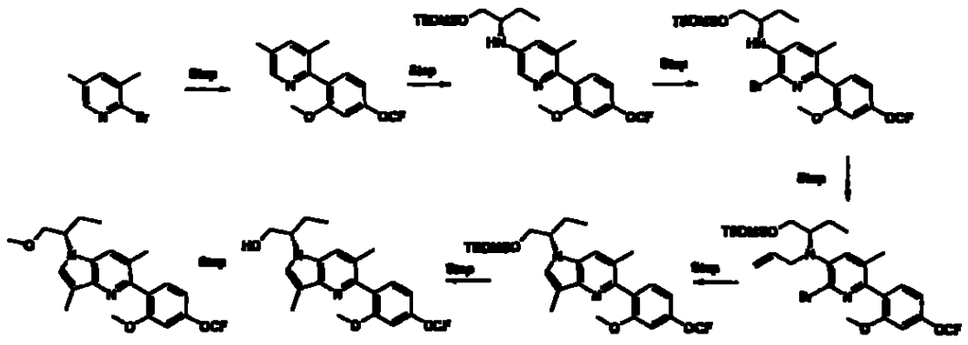
To a stirred solution of 5-(6-isopropyl-2-methoxy-pyridin 3-yl)-1-((S)-2-methoxy-1 methyl-ethyl)-6-methyl-1H pyrrolo[3,2-b]pyridine-3-carbaldehyde (0 13 g) in DCM (3 mL) is added hydroxylamine hydrochloride (36 mg) and Et_3N (0 07 mL) at RT The mixture is stirred at RT for 2 h and is diluted with EtOAc. The mixture is washed with water and dried over $MgSO_4$ The solvent is removed under reduced pressure to give 5-(6-isopropyl-2-methoxy pyridin-3 yl)-1-((S)-2-methoxy-1-methyl-ethyl)-6-methyl 1H pyrrolo[3,2-b]pyridine-3 carbaldehyde oxime as a mixture of syn-and anti- isomers LCMS Rt 1.38 min, m/z 397.21 (M+H) and Rt 1 44 min, m/z 397.21 (M+H)

Step D

To a solution of 5-(6-isopropyl-2-methoxy-pyridin 3 yl)-1-((S)-2 methoxy-1-methyl-ethyl)-6-methyl 1H-pyrrolo[3,2-b]pyridine-3-carbaldehyde oxime (0 136 g) in DCM (3 mL) is added Et_3N (0 47 mL) and methanesulfonyl chloride (0 13 mL) at RT After stirring at RT for 15 h, the mixture is poured into water (30 mL) and is extracted with EtOAc The extract is washed with water and brine and is dried over $MgSO_4$ After evaporation of the solvent, the residue is purified by flash column chromatography on silica gel to give 5-(6 isopropyl 2 methoxy-pyridin 3 yl)-1-((S)-2-methoxy-1-methyl-ethyl)-6-methyl 1H pyrrolo[3,2 b]pyridine-3-carbonitrile as amorphous. LCMS Rt 1 59 min m/z 379 19 (M+H)

EXAMPLE 28

Synthesis of (S)-2-[5-(2-methoxy-4-trifluoromethoxy-phenyl)-3,6-dimethyl-pyrrolo[3,2 b]pyridin-1 yl]-butan-1-ol and 1-((S)-1 methoxymethyl-propyl)-5-(2-meth xy-4-trifluoromethoxy phenyl)-3,6-dimethyl-1H pyrrolo[3,2 b]pyridine



Step A

A mixture of 2,5-dibromo-3 methyl pyridine (40g), 2-methoxy-4 trifluoromethoxy-1 phenylboronic acid (39 5g) and 2M K_2CO_3 (159ml) n toluene (300ml) is degassed with N_2 for 2 min followed by addition of $Pd(PPh_3)_4$ (5 5g) Th resulting mixture is stirred at 85 °C nder N_2 for overnight After reaction is complete, the mixture is poured into water (300ml) and extracted with ethyl acetate (3x150ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The product 5-bromo-2-(2 methoxy-4-trifluoromethoxy phenyl)-3-methyl-pyridine is obtained after flash chromatography (Hexane/EtOAc=20/1) TLC Rf 0 35 (Hexane/EtOAc=4/1)

Step B

A mixture of 5-bromo-2-(2-methoxy-4-trifluoromethoxy-phenyl)-3-methyl pyridine (1 31g), (S)-1-(*tert* Butyl-dimethyl-silanyloxymethyl)-propylamine (885mg), (+/)BINAP (181mg) and NaOBu (488mg) in toluene (10ml) is d gassed with N_2 for 2 min followed by addition of $Pd_2(dba)_3$ (133mg) The resulting mixture is stirred at 70 C under N_2 for 20 h The mixture s poured into water and extracted with EtOAc (3x30ml) The comb ned organic layers is washed with brine dried over Na_2SO_4 and evaporated The rude product is purified by flash chromatography (Hexane/EtOAc=3/1) m/z 485 5 (M+H)

Step C

257mg of [(S)-1-(*tert* Butyl-dimethyl-silanyloxymethyl)-propyl] [6-(2 methoxy-4 trifluoromethoxy-phenyl)-5-methyl pyridin 3 yl]-am ne is dissolved in CHCl (6ml) and NBS (95mg) is added at room temperature. After stirring at room temperature for 10 min the mixture is diluted with $CHCl_3$ and washed with H_2O brine and dried o er Na_2SO_4 The pure product 2-bromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-5 methyl-pyridin-3 yl] [(S)-1 (*tert* butyl-dimethyl-silanyloxymethyl)-propyl]-amine is obtained after column chromatography (Hexane/EtOAc=8/1) MS m/z 563 3/565 3 (M+H)

Step D

2 Bromo-6-(2 methoxy-4-trifluoromethoxy-phenyl)-5-methyl-pyridin 3 yl] [(S)-1 (*tert* butyl-dimethyl-silanyloxymethyl)-propyl]-amine (230mg) in anhydrous THF (6ml) is added 1M KOBu (1 03ml) followed by allyl bromide (71µl) at room temperature and the resulting mixture is allowed to stir at ambient temperature for 20 h The reaction is quenched by add ng 10 ml H_2O and the mixture is extracted with EtOAc (3x15ml) The combined organic

layers are washed with brine, dried over Na_2SO_4 and evaporated Flash column chromatography (Hexane/EtOAc=15/1) gives desired product TLC Rf 0 55 (Hexane/EtOAc=10/1)

Step E

A mixture of allyl-[2 bromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-5 methyl-pyridin-3-yl]-[(S)-1 (*tert*-butyl-dimethyl-silanyloxymethyl)-propyl]-amine (1 0g) tetrabutylammonium bromide (589mg), K_2CO_3 (687mg) in DMF (40ml) is degassed with N_2 for 3 min followed by addition of $Pd(OAc)_2$ (37mg) The resulting mixture is stirred at 80 °C for 18 h The reaction mixture is poured into water and extracted with EtOAc (3x25ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The crude product is purified by flash chromatography (Hexane/EtOAc=10/1) MS m/z 523 5 (M+H)

Step F

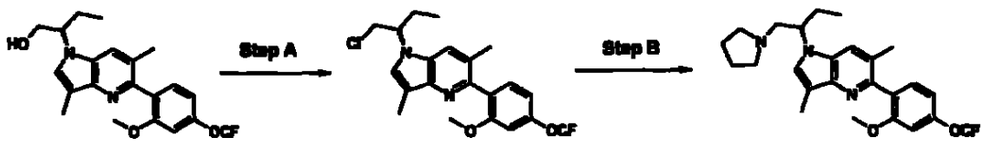
1-[(S)-1-(*tert* Butyl-dimethyl-silanyloxymethyl)-propyl]-5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine (1 19g) in THF (30ml) is added tetrabutylammonium fluoride (715mg) and the mixture is allowed to stir at room temperature for 30 min After the reaction is complete the solvent is removed and the crude mixture is purified by flash chromatography (CH_2Cl_2/MeOH=5/1) to gi e desired product. LC MS m/z 409 01 (M+H)

Step G

(S)-2-[5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin-1 yl]-butan 1-ol (60mg) in anhydrous THF (5ml) is added 60% NaH (29mg) and the mixture is allowed to stir at room temperature for 10 min before MeI (46µl) is added. After stirring at room temperature for 1 h, the reaction is quenched by adding water (15ml) The mixture is extracted with EtOAc (3x25ml), dried over Na_2SO_4 and evaporated The pure product 1-((S)-1-methoxymethyl-propyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyrid ne is obtained by flash column chromatography (Hexane/EtOAc=3/1) LC MS m/z 423 03 (M+H)

EXAMPLE 29

Synthesis of 1-((S)-1-chloromethyl-propyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridine and 5-(2 methoxy-4-trifluoromethoxy-phenyl)-3,6-dimethyl-1-((S)-1 pyrrolid n-1 ylmethyl-propyl)-1H pyrrolo[3,2-b]pyridine



Step A

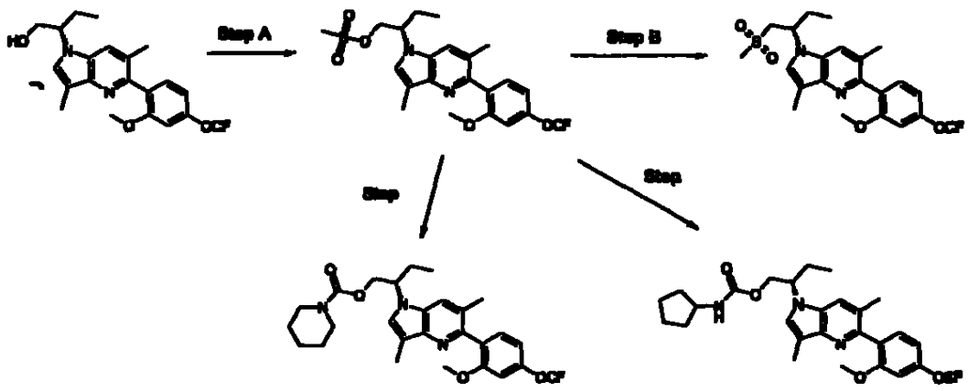
(S)-2 [5-(2 Methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3 2 b]pyridin 1 yl]-butan 1-ol (330mg) in $ClCH_2CH_2Cl$ (20ml) is cooled to 0 °C and $SOCl_2$ (1 77ml) is added dropwise The reaction is allowed to stir at room temperature for 12 h After removal of the solvent, the crude product s purified by flash column (Hexane/EtOAc=3/1) MS m/z 427 4 (M+H)

Step B

A mixture of 1-((S)-1-chloromethyl-propyl)-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl 1H-pyrrolo[3 2-b]pyridine (55mg) KI (15mg) and 0 8 ml pyrrolidine in DMSO (4ml) is heated to 120 C fo 19 h After starting material disappears, the mixture s poured into water and extracted with CH_2Cl (3x20ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The pure product 5-(2 methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl 1-((S)-1-pyrrolidin 1 ylmethyl-propyl)-1H pyrrolo[3,2 b]pyridineis obtained by preparative TLC purification (CH_2Cl_2/MeOH=15/1) LC MS m/z 462 10 (M+H)

EXAMPLE 30

Synthesis of methanesulfonic acid (S)-2-[5-(2-methoxy-4-trifluoromethoxy phenyl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin-1-yl]-butyl ester 1-((S)-1 methanesulfonylmethyl-propyl)-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3,6-dimethyl-1H pyrrolo[3,2-b]pyridine, piperidine-1-carboxylic acid (S)-2-[5-(2-methoxy-4-trifluoromethoxy phenyl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl]-butyl ester and cyclopentyl-carbamic acid (S)-2-[5-(2-methoxy-4-trifluoromethoxy phenyl)-3,6-dimethyl-pyrrolo[3,2 b]pyridin-1 yl] butyl ester



Step A

(S)-2-[5-(2 Methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl pyrrolo[3,2-b]pyridin-1 yl] butan-1-ol (120mg) in CH_2Cl_2 (6ml) is cooled to 0 °C and the mixture is added triethylamine (82µl) followed by methanesulfonyl chloride (45µl) The mixture is allowed to stir at 0 °C to roomf temperature for 16 h After removal of the solvent, the crude mixture is purified by column chromatography (CH_2Cl_2/MeOH=12/1) LC MS m/z 486 99 (M+H)

Step B

A mixture of methanesulfonic acid (S)-2 [5-(2 methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl-pyrrolo[3,.. b]pyridin 1 yl]-butyl ester (39mg), KI (5mg) and CH_3SO_2Na (100mg) in DMSO (2ml) were heated to 80 °C for 17 h The mixture is poured into water and extracted with EtOAc (3x15ml) The combined organic layers are washed with brine, dried over Na_2SO and evaporated The pure product 1-((S)-1-methanesulfonylmethyl-propyl)-5 (2-methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl 1H-pyrrolo[3,2-b]pyridine is obtained by preparative TLC purification (Hexane/EtOAc=1/1) LC MS m/z 471 03 (M+H)

Step C

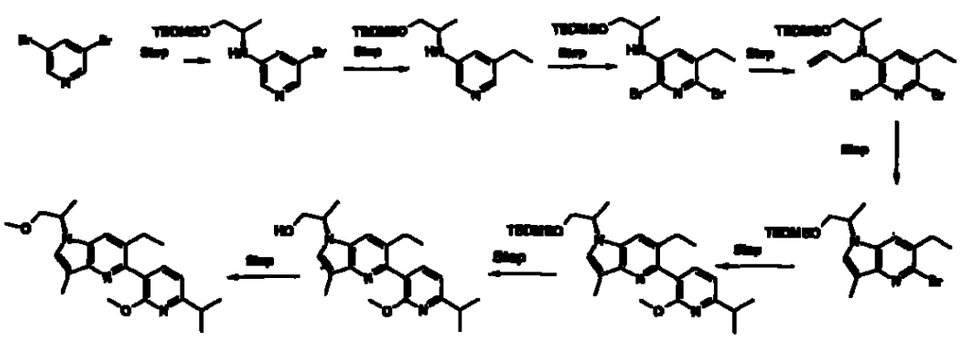
2 ml of methanesulfonic acid (S)-2 [5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3 2 b]pyridin 1 yl]-butyl ester (0 02 M in DMSO) is added 0.2 ml of piperidine (0.2 M in toluene), followed by $NaHCO_3$ (50mg) and KI (10mg) The resulting mixture is shaken at 80 °C for 18 h The mixture is diluted with water extracted with EtOAc (2x10ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The pure product piperidine-1-carboxylic acid (S)-2 [5-(2-methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin 1 yl] butyl ester is obtained by preparative TLC purification (Hexane/EtOAc=1/1) LC MS m/z 520 11 (M+H)

Step D

2 ml of methanesulfonic acid (S)-2-[5-(2-methoxy-4-trifl oromethoxy-phenyl)-3 6-d methyl-pyrrolo[3 2-b]pyridin 1 yl]-butyl ester (0 02 M in DMSO) is added 0 2 ml of cyclopentylamine (0.2 M in toluene) followed by $NaHCO_3$ (50mg) and KI (10mg) The resulting mixture is shaken at 80 °C for 18 h The mixture is diluted with water extracted with EtOAc (2x10ml) The combined organic layers are washed with brine, dried over Na_2SO and evaporated The pure product cyclopentyl-carbamic acid (S)-2 [5 (2-methoxy-4-trifl oromethoxy phenyl)-3 6-d methyl-pyrrolo[3 2 b]pyrid n 1 yl]-butyl ester is obtained by preparative TLC purification (Hexane/EtOAc=1/1) LC MS m/z 520 12 (M+H)

EXAMPLE 31

Synthesis of (R)-2-[6-ethyl-5-(6-isopropyl-2-methoxy pyridin-3-yl)-3-methyl-pyrrol [3,2-b]pyridin 1 yl] propan-1-ol a d 6-ethyl-5-(6-isopropyl-2-methoxy pyridin-3-yl)-1-((R)-2-methoxy-1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridine



Step A

A mixture of 3,5-dibromopyridine (30.3g), (R)-2-(*tert* butyl-dimethyl-silanylo xy)-1-methyl-ethylamine (25 4g), (+/)BINAP (6 37g) and NaOB (17 18g) in toluene (300ml) is degassed for 5 min, followed by addition of $Pd_2(dba)_3$ (4 68g) The resulting mixture is stirred at 70 °C for 4 h The reaction mixture is poured into water (200ml), extracted with EtOAc(3x150ml). The combined organic layers are washed with brine dried over Na_2SO_4 and evaporated. The desired product is obtained after flash column chromatography (Hexane/EtOAc=3/1) LC MS m/z 347.24 (M+H)

Step B

A mixture of (5-bromo-pyridin 3 yl)-[(R)-2-(*tert* butyl-dimethyl-silanyloxy)-1-methyl ethyl]-amine (22 74g) 2M K_2CO_3 (99ml) and 165 ml Et_3B (1M in hexane) in toluene (200ml) is degassed with N_2 for 5 min, followed by addition of $Pd(PPh_3)_4$ (3 8g) The resulting mixture is allowed to stir at 110 °C for 16 h The mixture is poured into water (200ml), extracted with EtOAc (3x200ml), dried over Na_2SO_4 and vaporated The crude product [(R)-2-(*t rt* butyl-dimethyl-silanyloxy)-1 methyl-ethyl]-(5-ethyl-pyridin 3 yl)-amine is used for next step w thout further purification LC MS m/z 295 14 (M+H)

Step C

Crude product from last step is dissolved in $CHCl_3$ (250ml) and NBS (2 eq) is added in one portion at room temperature After stirring at room temperature for 15 min, the solution is washed with water (2x100ml) The organic phase is dried over Na_2SO and evaporated The crude product is purified by flash chromatography (Hexane/EtOAc=8/1) LC MS m/z 451 12/453 11 (M+H)

Step D

(R)-2-(*tert* Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-(2 6-dibromo-5-ethyl pyridin 3 yl)-amine (11 5g) in anhydrous THF(180ml) is added 1M $KOBu^t$ (50 9ml) followed by allyl iodide (3.48ml) The resulting mixture is allowed to stir at room temperature for 22 h before t is quenched w th water (100ml) The mixture is extracted with EtOAc (3x150ml) The combined organic layers are washed with brine dried over Na_2SO_4 and evaporated The pure product allyl-[(R)-2-(*tert*-butyl-dimethyl-silanyloxy)-1 methyl-ethyl]-(2 6-dibromo-5-ethyl-

pyrid n 3 yl)-amine is obtained after column chromatography (Hexane/EtOAc=10/1) TLC Rf 0 6 (Hexane/EtOAc=10/1)

Step E

A mixture of allyl [(R)-2-(*tert* butyl-dimethyl-silanyloxy) 1 methyl-ethyl]-(2,6-d bromo-5 ethyl pyridin 3 yl)-amine (8 3g), tetrabutylammonium bromide (6 0g), K_2CO_3 (6 99g) in DMF (100ml) is degassed for 3 min, followed by addition of $Pd(OAc)_2$ The resulting m xture is stirred at 80 °C for 18 h After the mixture is complete the mixture is poured into H_2O (200ml) extracted with EtOAc(3x100 ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The crude product is p rified by flash column chromatography (Hexane/EtOAc=10/1) TLC Rf 0 5 (Hexane/EtOAc=4/1)

Step F

A mixture of 5 bromo-1 [(R) 2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl ethyl]-6-ethyl 3 methyl 1H pyrrol [3,2 b]pyrid n (2 21g) 2M K_2CO_3 (5 4ml), and 2-methoxy-6 isopropyl 3 pyridylboronic acid (1 20g) in DME (25 ml) is degassed w th N_2 for 2 min, followed by addition of $Pd(PPh_3)_4$ The resulting mixture is stirred at 85 °C for 16 h before it is poured nto water (80ml) and extracted with EtOAc (3x30ml) The combined organ c layers are washed w th brine, dried over Na_2SO and evaporated Flash column chromatography (Hexane/EtOAc=6/1) gives the pure product 1-[(R) 2-(*tert* butyl-d methyl sila yloxy)-1 methyl-ethyl]-6-ethyl 5-(6-isopropyl 2-methoxy pyridin 3 yl)-3 methyl 1H-pyrrolo[3,2 b]pyrid ne. LC MS m/z 482 18 (M+H)

Step G

1-[(R) 2-(*tert* Butyl-dimethyl-silanyloxy)-1-methyl-ethyl]-6-ethyl 5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 methyl 1H pyrrolo[3 b]pyrid (1 87g) in THF (60ml) s added tetrabutylammon um fluoride (1 53g) and the mixture is allowed to stir at room temperature for 15 min before the solvent is evaporated The crude product is purified by flash chromatography (Hexane/EtOAc=1/1) MS m/z 368 4 (M+H)

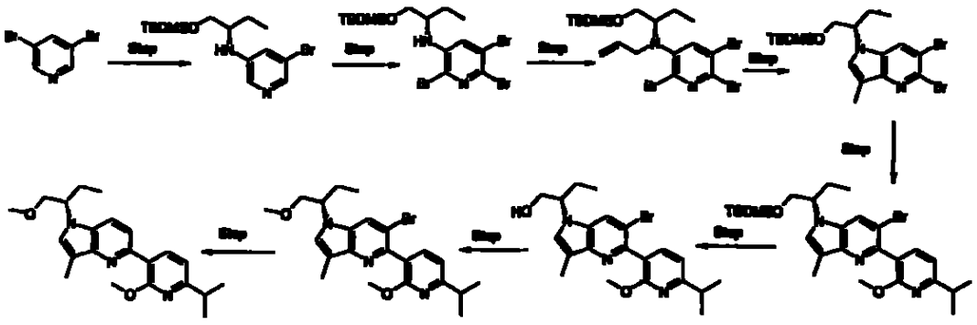
Step H

(R)-2 [6 Ethyl 5-(6-isopropyl-2-methoxy pyridin 3 yl)-3 methyl-pyrrolo[3,2 b]pyrid n 1 yl] propan 1-ol (1 15g) in anhydrous THF (40ml) is added NaH (627mg) and the mixture is

stirred at room temperature for 5 min before MeI (978µl) is added The reaction mixture is stirred at room temperature for 3 h and then quenched with H_2O (50ml) and extracted with EtOAc (3x40ml) The combined organic layers are washed with brine dried over Na_2SO_4 and evaporated The pure product 6-ethyl 5-(6-isopropyl-2-methoxy pyridin 3 yl)-1-((R)-2 methoxy 1-methyl-ethyl)-3-methyl 1H-pyrrolo[3,2 b]pyridine is obtained by flash chromatography (Hexane/EtOAc=4/1) LC MS m/z 382 44 (M+H)

EXAMPLE 32

Synthesis of (S)-2-[6-bromo-5-(6-isopropyl-2-methoxy pyridin-3-yl)-3-methyl pyrrolo[3,2-b]pyridi 1 yl] butan 1-ol 6-bromo-5-(6-isopropyl-2 methoxy-pyridin-3-yl)-1-((S)-1 methoxymethyl-propyl)-3-methyl-1H pyrrolo[3,2-b]pyridine and 5-(6-isopropyl-2-methoxy pyrid n-3-yl)-1-((S)-2-methoxy 1 methyl-propyl)-3-methyl-1H pyrrolo[3,2-b]pyrid



Step A

A mixture of 3 5-dibromopyridine (50g), (S)-1-(*tert*-butyl-dimethyl-silanylo xymethyl)-propylamine (43 68g) (+/)BINAP (10 51g) and NaOBu (28 35g) in toluene (400ml) is degassed w th N_2 for 5 min, followed by addition of $Pd_2(dba)_3$ (7 73g) The resulting mixture is stirred at 70 °C for 23 h The reaction mixture is poured into water (200ml) extracted with EtOAc(3x200 ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The desired product is obtained after flash column chromatography (Hexane/EtOAc=5/1) TLC Rf 0 4 (Hexane/EtOAc=4/1)

Step B

(5 Bromo-pyridin 3 yl)-[(S)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-propyl]-amine (7 58g) in $CHCl_3$ (150ml) is added NBS (7 51g) and the mixture is stirred at room temperature for 15

min before it is washed with H_2O (2x50 ml) The organic layer is dried over Na_2SO nd evaporated The crude product is purified by column chromatography (Hexane/EtOAc=10/1) TLC Rf 0 7 (Hexane/EtOAc=4/1)

Step C

(S)-1-(*tert* Butyl-dimethyl-silanyloxymethyl)-propyl]-(2,5 6-tribromo-pyridin 3 yl)-amine (6 33g) in THF (60ml) is added 24.5 ml KOBu (1 M in THF) followed by allyl iodide (1 68ml) The resulting mixture is stirred at room temperature for 24 h before it is quenched with water (60ml) The mixture is extracted with EtOAc (3x30ml) and the combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The pure product allyl [(S)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-propyl]-(2,5 6-tribromo-pyridin-3 yl)-amine is obtained by flash column chromatography (Hexane/EtOAc=15/1) TLC Rf 0 6 (Hexane/EtOAc=10/1)

Step D

A mixture of allyl [(S)-1-(*tert* b tyl-dimethyl-silanyloxymethyl)-propyl]-(2 5 6-tribromo-pyridin 3 yl)-amine (5 81g), tetrabutylammonium bromide (3 7g), K_2CO_3 (4 32g) in DMF (25ml) is degassed with N_2 for 2 min, followed by addition of $Pd(OAc)_2$ (214mg) The resultmg mixture s stirred at 80 °C for 1 5 h before it is poured into water (50ml), and extracted with EtOAc (3x30ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The crude product is purified by flash column chromatography (Hexane/EtOAc=10/1) TLC Rf 0 3 (Hexane/EtOAc=10/1)

Step E

A mixture of 5 6-dibromo-1 [(S)-1 (*tert* butyl-dimethyl-silanyloxymethyl)-propyl] 3 methyl 1H-pyrrolo[3 2 b]pyridine (3 66g) 2M K_2CO_3 (22ml) 2 methoxy-6-isopropyl 3 pyridylboronic ac d (1 64g) in DME is degassed with N_2 for 5 mm followed by addition of $Pd(PPh_3)_4$ (444mg) The resulting mixture is allowed to stir at 85 °C for 3 5 h before it is poured into H_2O (50ml), extracted with EtOAc (3x40ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The pure product 6-bromo-1 [(S)-1 (*tert* butyl-dimethyl-silanyloxymethyl)-propyl] 5-(6-isopropyl-2-methoxy pyridin 3 yl)-3 methyl 1H-pyrrolo[3,2 b]pyridine is obtained by flash col mn chromatography (Hexane/EtOAc=8/1) LC MS m/z 547.3 (M+H)

Step F

6-Bromo-1 [(S)-1-(*tert*-butyl-dimethyl silanyloxymethyl)-propyl] 5-(6-isopropyl 2-methoxy-pyridin-3 yl)-3-methyl 1H-pyrrolo[3,2 b]pyridine (2 74g) in THF (50ml) is added tetrabutylammonium fluoride (1 97g) and the resulting mixture is stirred at room temperature for 2h After removal of the solvent, the crude product is purified by column chromatography (Hexane/EtOAc=1/1) LC MS m/z 433 35 (M+H)

Step G

A mixture of (S)-2-[6-bromo-5-(6-isopropyl 2-methoxy-pyridin 3 yl)-3-methyl-pyrrolo[3,2 b]pyridin 1 yl]-butan 1-ol (2 0g) in THF (40ml) is added 60% NaH (463mg) and the mixture is stirred at 0 °C for 10 min before MeI (578µl) is added After stirring at room temperature for 3.5 h, the mixture is poured into water (50ml) and extracted with EtOAc(3x30ml) The combined organic layers are washed with brine dried over Na_2SO_4 and evaporated Column chromatography (Hexane/EtOAc=6/1) gives the pure product 6-bromo-5-(6-isopropyl 2 methoxy-pyridin-3 yl)-1 ((S)-1-methoxymethyl-propyl)-3 methyl 1H pyrrolo[3 2 b]pyridine LC MS m/z.447 37 (M+H)

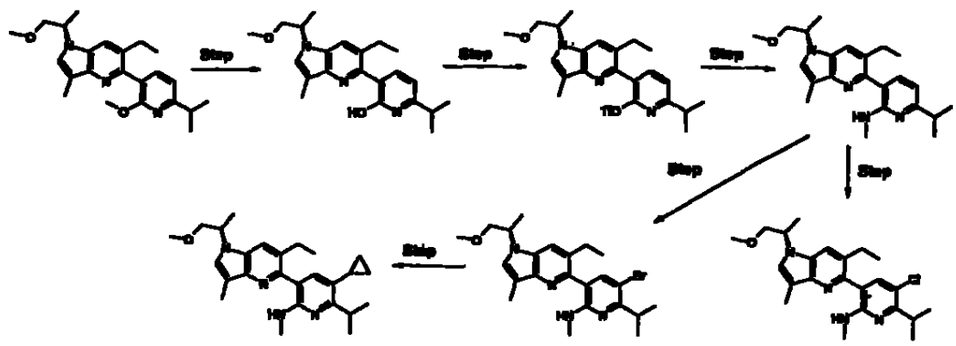
Step H

6-Bromo-5-(6-isopropyl 2-methoxy pyridin 3 yl)-1-((S)-1 methoxymethyl propyl)-3 methyl 1H-pyrrolo[3,2-b]pyridine (450mg) in EtOH (30ml) is added 10% Pd/C (200mg) under N_2 and the mixture is shaken under 40 psi H_2 pressure for 48 h the catalyst is removed by filtering through celite After removal of solvent, the desired product 5-(6-isopropyl 2-methoxy pyridin-3 yl)-1-((S)-2 methoxy 1 methyl-propyl)-3-methyl-1H pyrrolo[3,2-b]pyridine is obtained MS m/z 368 4 (M+H)

EXAMPLE 33

Synthesis of {3-[6-ethyl-1-((R)-2-methoxy-1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2 b]pyridin-5-yl]-6-isopropyl pyridin-2-yl} methyl-amine 5-chloro-3-[6-ethyl-1-((R)-2-methoxy 1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2 b]pyridin-5-yl]-6-isopropyl-pyridin 2-yl} methyl-amine {5-bromo-3-[6-ethyl-1-((R)-2-methoxy 1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridin-5-yl]-6-isopropyl-pyridin 2-yl} methyl-amine and {5-

cyclopropyl-3-[6-ethyl-1-((R)-2-methoxy 1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridin-5-yl]-6-isopropyl-pyridin-2-yl}methyl-amine



Step A

A mixture of 6-ethyl 5-(6 isopropyl 2 methoxy pyridin 3 yl)-1-((R)-2-methoxy 1 methyl ethyl)-3-methyl-1H pyrrolo[3 2 b]pyridine (1 02g) and 6N HCl (20ml) is heated to 75 C for 20 h The mixture is cooled down to 0 °C nd neutral zed w th 10 N N OH to PH>10 The bas solution is extracted with CH_2Cl_2 (3x40ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The crude product 3 [6-ethyl 1-((R)-2 methoxy 1 methyl-ethyl)-3-methyl 1H-pyrrolo[3,2-b]pyridin 5-yl] 6-isopropyl-pyridin-2-ol is used for next step without further purif cation TLC Rf 0.2 (CH Cl_2/MeOH=12/1)

Step B

Crude product from previo s step is diasolved in CH_2Cl_2 (30 ml) and the mixture is cooled to 0 °C followed by addition of triethylamine (1 11ml) and trifluoromethanesulfonic anhydride (898 µl) After stirring at room temperature for 3 h, the mixture is poured into H_2O (30 ml) and extracted with EtOAc (3x30ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated The pure des red product trifluoro-methanesulfon c ac d 3 [6-ethyl 1-((R)-2-methoxy 1 methyl-ethyl)-3 methyl-1H-pyrrolo[3 2 b]pyridin 5 yl]-6-sopropyl-pyridin 2 yl ester is obtained by flash column chromatography (CH_2Cl_2/MeOH=6/1) TLC Rf 0 4 (CH_2Cl_2/MeOH=12/1)

Step C

A mixture of trifluoro-methanesulfonic acid 3 [6-ethyl 1-((R)-2 methoxy 1 methyl-ethyl)-3 methyl 1H-pyrrolo[3 2-b]pyrid n 5 yl]-6-isopropyl pyridin 2 yl ester (200mg) and NMP (6ml) is added l ml M NH (4M NMP) and the m xth re heated to 80 °C for 20 h Th

mixture is poured into water (20ml), extracted with EtOAc (3x15ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated. The pure product is obtained after preparative TLC purification (Hexane/EtOAc=2/1) LC MS m/z 381.45 (M+H)

Step D

{3 [6-Ethyl-1-((R)-2-methoxy-1-methyl-ethyl)-3 methyl-1H-pyrrolo[3 2 b]pyridin 5 yl]-6 isopropyl-pyridin-2 yl}-methyl-amine (60mg) in $CHCl_3$ (5ml) is added N-chlorosuccinimide (23mg) and the mixture is heated at 60 °C for 5 h. After the reaction is complete, the solvent is removed and the crude product is purified by preparative TLC (Hexane/EtOAc=4/1) to give 5-chloro-3 [6-ethyl 1-((R)-2 methoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}methyl-amine. MS m/z 415.4 (M+H)

Step E

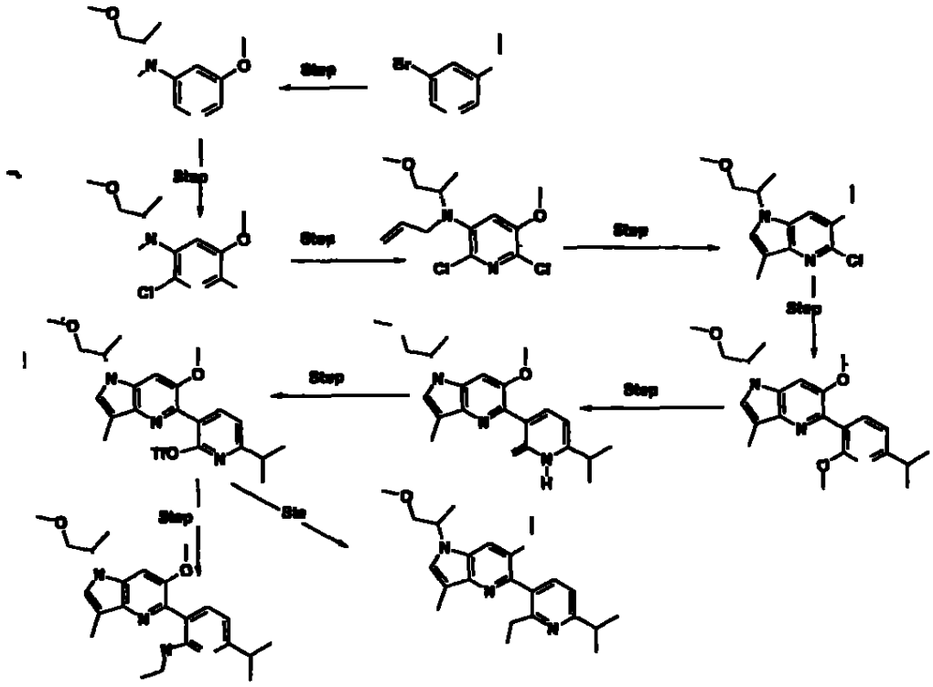
A mixture of {3 [6-Ethyl-1-((R)-2-methoxy 1-methyl-ethyl)-3-methyl 1H-pyrrolo[3,2 b]pyridin-5 yl]-6-isopropyl pyridin 2 yl} methyl-amine (130mg) in CH_3CN (5ml) is cooled to 0 °C followed by addition of NBS (61mg) The resulting mixture is stirred at 0 °C for 30 min and then it is diluted with H_2O (20ml), extracted with EtOAc(3x25 ml) The combined organic layers are washed with brine, dried over Na_2SO_4 and evaporated Flash column chromatography (Hexane/EtOAc=8/1) gives pure product {5-bromo-3 [6-ethyl-1-((R)-2 methoxy 1-methyl-ethyl)-3-methyl 1H-pyrrolo[3,2-b]pyridin 5 yl]-6-isopropyl-pyridin 2 yl} methyl-amine LC MS m/z 461 35 (M+H)

Step F

A mixture of {5-bromo-3 [6-ethyl-1-((R)-2 methoxy 1 methyl-ethyl)-3-methyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl-pyridin 2 yl} methyl-amine (60mg) 2M K_2CO_3 (1ml), cyclopropyl boronic acid (56mg) in toluene (5ml) is degassed with N_2 for 2 min, followed by addition of $Pd(PPh_3)_4$ (15mg) The resulting mixture is stirred at 110 °C for 16 h before it is poured into water and extracted with EtOAc(3x15ml) The combined organic layers are washed with brine dried over Na_2SO_4 and evaporated The pure product {5 cyclopropyl 3 [6-ethyl 1-((R)-2 methoxy-1-methyl-ethyl)-3-methyl 1H-pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl-pyridin 2 yl}methyl-amine is obtained after preparative TLC purification (CH_2Cl_2/MeOH=20/1) MS m/z 421 5 (M+H)

EXAMPLE 34

Synthesis of thyl-{6-isopropyl-3 [6-methoxy 1-((S)-2-methoxy 1-methyl-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridi 5-yl] pyridin 2 yl}ami e and 5-(2-ethyl-6-isopropyl-pyridin-3-yl)-6-methoxy 1-((S)-2-m thoxy 1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridine



Step A

Analogous to the preparat on of (5 bromo-pyridin 3 yl)-[(S) 1 (*tert* butyl-dimethyl-silanyloxymethyl)-propyl]-amine the palladium mediated am nat on of 3 bromo-5 methoxypyridine (4 76g) with (S)-1-methoxy-2 propylamine (4 4 mL) gives, afte purification on silica gel ((S)-2 m thoxy 1 methyl-ethyl)-(5 methoxy pyridin 3 yl)-am e. LCMS m/z 197 1 (M+H) Rt 2 47 mins

Step B

The chlo ination of ((S) 2 methoxy 1 methyl-ethyl)-(5-methoxy-pyridin 3 yl)-amine (5 0g) with N-chlorosuccinimide (7 21g) gives, after purification on silica gel (2 6-d chloro-5

methoxy pyridin 3 yl)-((S)-2-methoxy 1-methyl-ethyl)-amine LCMS m/z 265.2/267 1/269 1 (M+H) Rt 3 03 mins

Step C

Analogous to the synthesis of allyl [(S) 1 (*tert*-butyl-dimethyl silanyloxymethyl)-propyl] (2 5 6 tr bromo-pyridin-3 yl)-amine the allylation of (2 6-dichloro-5 methoxy-pyridin 3 yl)-((S)-2 methoxy 1 methyl-ethyl)-amine (5 38g) with allyl iodide (4 0 mL) affords, after purification on s lica gel allyl-(2,6-dichloro-5 methoxy-pyridin 3 yl)-((S)-2-methoxy 1 methyl-ethyl)-amine LCMS m/z 305 1/307 1/309 0 (M+H) Rt 3 49 mins

Step D

Analogous to the sy thes s of 5 6-d bromo-1 [(S)-1-(*tert* butyl-dim thyl silanyloxymethyl)-propyl] 3-methyl 1H pyrrolo[3,2 b]pyridine the palladium mediated cyclization of allyl-(2 6-dichloro-5 methoxy-pyridin 3 yl)-((S)-2-methoxy 1 methyl-ethyl)-amine (5 13g) affords, after purification on silica gel 5-chloro-6-methoxy-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]py id ne LCMS m/z 269 1/271 1 (M+H) Rt 2 41 mins

Step E

Analogous to the synthesis of 6-bromo-1 [(S)-1-(*t t* b tyl-dim thyl s lanyloxymethyl)-propyl] 5 (6 isopropyl 2 m thoxy-pyridin 3 yl) 3 methyl 1H pyrrolo[3,2 b]pyridine the palladium mediated coupling of 5-chloro-6-methoxy 1-((S)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2-b]pyridine (1 9g) with 6-isopropyl 2 methoxy 3 py dineboronic ac d (1 79g) affords, after purification on silica gel 5-(6- sopropyl 2-methoxy pyridin 3 yl)-6-m thoxy 1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridine LCMS m/z 384 2 (M+H) Rt 2 40 mins

St p F

A solut on of 5 (6-isopropyl 2 methoxy-pyridin 3 yl)-6-methoxy 1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridine (890mg) n conc ntrated hydrochlor c acid (60 mL, 37%) is heated at 55 °C for 16 ho rs The res lt ng sol tion is neutralized w th sodium bicarbonate and d luted with a little water The mixture s extracted with dichloromethane (4x50mL) and dr ed over magnesium sulfate Evaporation of the solvent followed by trituration with d ethyl ether g ves 6-isopropyl 3 [6 methoxy 1-((S)-2 methoxy

1-methyl-ethyl)-3-methyl 1H-pyrrolo[3 2 b]pyridin 5 yl] pyrid 2-ol LCMS m/z 370 2 (M+H) Rt 2 01 min

Step G

Analogous to the synthesis of trifluoro-methanesulfo ic ac d 3-(3 6-d methyl 1 propyl 1H pyrrolo[3 2 b]pyrid n 5 yl)-6 isopropyl-pyridin 2 yl ester the reaction of 6-isopropyl 3 [6 methoxy 1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid n 5 yl] pyridi 2-ol (200mg) with triflic anhydride (0 11mL) in the presence of triethyl amine (0 136mL) gi es after purificat on on silica gel trifluoro-methanesulfon c acid 6-isopropyl 3 [6-methoxy 1-((S)-2-methoxy 1-methyl-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyridin 5 yl] pyridin 2 yl ester LCMS m/z 502 1 (M+H) Rt = 3 29 mins

Step H

Analogous to the preparat on of [3-(3 6-dimethyl 1-propyl 1H pyrrolo[3 2 b]pyridi 5 yl)-6 sopropyl-pyrid n-2 yl]-ethyl-am ne the react on of trifluoro-meth nes lfon acid 6-isopropyl 3 [6-methoxy 1-((S)-2 methoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]py id 5 yl] pyrid 2 yl este (70mg) with ethyl am solution THF (0 7mL, 2M) affords, afte purificat on on s l ca gel gives ethyl {6- sopropyl 3 [6 methoxy 1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H-pyrrolo[3 2-b]pyridin 5 yl] pyridin 2 yl}-amine LCMS m/z 397 3 (M+H) Rt = 2 14 m ns.

Step I

Analogous to the preparation of 5-(2-ethyl-6-isopropyl pyridin 3 yl) 3 6-dimethyl 1 propyl 1H-pyrrolo[3 2 b]pyridine the react on of trifluoro-methanesulfoni acid 6- sopropyl 3 [6-methoxy 1-((S)-2-methoxy 1-methyl-ethyl)-3 methyl 1H-pyrrolo[3 2 b]pyridin 5 yl] pyrid n 2 yl ester (180mg) with triethylborane solution n hexanes (1 44mL, 1 0M) ffords after purification on silica gel 5-(2-ethyl-6-isopropyl pyrid n 3 yl) 6 methoxy 1-((S)-2 methoxy 1-methyl-ethyl) 3 methyl 1H pyrrolo[3 2 b]pyridine LCMS m/z 387 3 (M+H) Rt = 1 94 mins

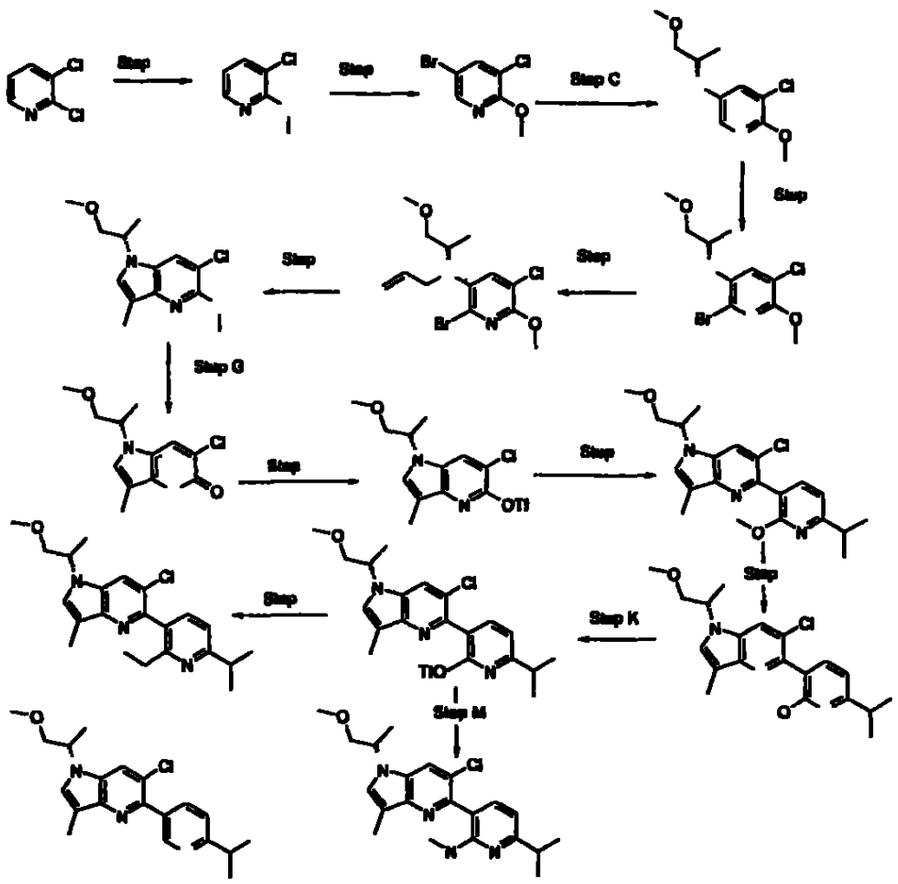
Replac g the amine sed in step H of Example 34 with arious other amine reagents, the following compounds are synthesized

{6-Isopropyl-3 [6-methoxy 1-((S)-2 methoxy-1 methyl-ethyl) 3-methyl 1H py rolo[3,2 b]pyridin 5 yl]-pyridin 2 yl}-dimethyl-amine Rt 1 97min m/z 397.2(M+H)

{6-Isopropyl 3 [6-methoxy 1-((S)-2 methoxy-1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl]-pyridin 2 yl}-methyl-amine Rt 1.93min m/z 383.3(M+H)

EXAMPLE 35

Synthesis of 6-chloro-5-(2-ethyl-6-isopropyl-pyridin-3-yl)-1-((S)-2 methoxy-1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridine, 6-Chloro-5-(6-isopropyl-pyridin-3-yl)-1 ((S)-2-methoxy-1 methyl-ethyl)-3 methyl-1H pyrrolo[3,2-b]pyridine and {3-[6-chloro-1 ((S)-2-m thoxy 1 m thyl-ethyl)-3-methyl-1H py rolo[3,2 b]pyrid 5-yl]-6-isopropyl-pyridin-2 yl} m thyl-amin



Step A

Similar to a procedure by Testaferre et al (Tetrahedron 41 No7 1373 1384 1985) a suspension of 2 3-dichloropyridine (10g) in sodium methoxide solution in methanol (62mL, 25%) is heated to 55°C for 15 hours The suspension is filtered and the filtrate is evaporated to low volume The mixture is diluted with saturated brin extracted with diethyl ether (3x50mL) and dried over magnesium sulfate Evaporation directly gives 3-chloro-2 methoxy-pyridine LCMS m/z 144 0/146 0 (M+H) Rt 2 29 mins

Step B

Similar to a procedure by Bargar et al (J Het Chem 22 1583 1985) a stirred suspension of 3-chloro-2 methoxy-pyridine (9 3g) and sodium acetate (5 4g) in glacial acetic acid (30mL) is treated with bromine (6 7mL) dropwise over 15 min After the exotherm has subsided, the mixture is heated at 80°C for one hour The reaction mixture is cooled to room temperature and diluted with ether (200mL) and washed with sodium hydroxide solution (1M) and sodium thiosulphate solution (100mL, 2M) The ether layer is dried over magnesium sulfate and evaporated to give 5 bromo-3 chloro 2 methoxy pyridine The compound is used with further purification in the next reactio

Step C

Analogous to the preparation of ((S)-2-methoxy-1-methyl-ethyl)-(5 methoxy-pyridin 3 yl)-amine, the palladium mediated amination of 5 bromo-3-chloro-2 methoxy pyridine (4 0g) with (S) 1 methoxy 2 propylam (2 1 mL) affords, after purification on silica gel (5 chloro-6-methoxy-pyridin 3 yl)-((S)-2 methoxy 1 methyl-ethyl)-amin LCMS m/z 231 1/233 1 (M+H) Rt 2 19 mins

Step D

Analogous to the synthes s of (R)-2-(*tert*-butyl-dimethyl l nyloxy)-1 methyl-ethyl]-(2 6 dibromo-5-ethyl pyridin 3 yl)-amine, the bromination of (5-chloro-6 methoxy pyridin-3 yl)-((S)-2 methoxy 1-methyl-ethyl)-amine (1 350g) with N bromosucc imide (782mg) gives, after purification on silica gel (2 bromo-5-chloro-6 methoxy pyridin-3 yl)-((S)-2-methoxy 1 methyl-ethyl)-am ne LCMS m/z 309 0/311 0/312 0 (M+H) Rt 3 00 mins

Step E

Analogous to the synthesis of allyl [(S)-1-(*tert* butyl-dimethyl-silanyloxymethyl)-propyl] (2 5 6-tribromo-pyrid n-3 yl)-amine the allylation of (2-bromo-5-chloro-6-methoxy pyridin-3 yl)-((S) 2 methoxy-1 methyl-ethyl)-amine (1 05g) w th allyl iodide (0 68 mL) gives, after purification on silica gel allyl-(2 bromo-5-chloro-6-methoxy-pyridin 3 yl)-((S)-2 methoxy 1 methyl-ethyl)-amine LCMS m/z 349 0/351 0/353 0 (M+H) Rt 3 32 mins

Step F

Analogous to the synthesis of 5-chloro-6-methoxy-1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2-b]pyridine the palladium mediated cyclization of allyl-(2-bromo-5 chloro-6-methoxy pyridin 3 yl)-((S)-2-methoxy 1-methyl-ethyl)-amine (1 12g) affords, after purification on s lica gel affords 6-chloro-5 methoxy 1-((S)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridine LCMS m/z 269 1/271 1 (M+H) Rt 2 92 mins

Step G

6-Chloro-5 methoxy 1-((S)-2 methoxy-1-methyl-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyrid ne (153mg) is reacted with sodi m th omethoxide (800mg) Evaporat on of the solvent extracts and triturat on of the rude res due with diethyl ether gives 6-chloro-1-((S)-2-methoxy 1 methyl-ethyl) 3 methyl 1 4-d hydro-pyrrolo[3,2-b]py idi 5-on LCMS m/z 255 1/257 1 (M+H) Rt 2 03 mins

Step H

Analogous to the synthesis of trifluoro-methanesulfonic acid 6-isopropyl 3 [6 methoxy 1 ((S)-2 methoxy 1 m thyl-ethyl) 3 methyl 1H pyrrolo[3,2-b]pyr din 5 yl]-pyrid n 2 yl ester reaction of 6-chloro 1-((S) 2 m thoxy-1 methyl ethyl) 3 n ethyl 1 4-d hydro pyrrolo[3,2 b]pyridin 5-one (340mg) with tr flic anhydride (0.27mL) n the prese ce of triethyl amine (0 34mL) affords, after p rification on silica gel trifluoro-methanesulfonic acid 6-chloro-1 ((S)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]py idin 5 yl ester LCMS m/z 387 0/389 0 (M+H) Rt = 3 22 mins

Step I

Analogous to the synthesis of 5-(6-isopropyl 2-methoxy-pyridin 3 yl)-6-methoxy 1-((S)-2 methoxy 1 methyl-ethyl)-3-m thyl 1H pyrrolo[3,2-b]pyrid ne the palladium mediated

coupl ng of trifluoro-methanesulfonic ac d 6-chloro-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid 5 yl ester (500mg) with 6-isopropyl 2 methoxy 3 pyrid neboronic acid (430mg) affords, after purification on s l ca gel 6-chloro-5-(6 isopropyl 2 methoxy-pyridin 3 yl)-1-((S) 2-methoxy 1 methyl-ethyl) 3-methyl 1H pyrrolo[3 2 b]pyridine LCMS m/z 388 2/390 2 (M+H) Rt 3 15 mins

Step T

Analogous to the preparat on of 6-chloro-1-((S) 2 methoxy 1 methyl-ethyl) 3-methyl 1 4 dihydro-pyrrolo[3 2 b]pyridin 5-one, 6-chloro-5-(6- sopropyl-2 methoxy pyrid n-3 yl)-1 ((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridine (300mg) is reacted with sodium thiomethox de (500mg) E aporation of the sol ent extracts and trituration of the crude residue with d ethyl ether gives 3 [6-chloro-1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid n 5 yl]-6 sopropyl 1H py d 2-one LCMS m/z 374 2/376 2 (M+H) Rt 2 23 m s

Step K

A alogo s to th preparatio of trifl oro-methanes lfonic ac d 6 isopropyl 3 [6-methoxy 1 ((S)-2 metho y 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2-b]pyrid n 5 yl]-pyridin 2 yl ester react on of 3 [6-chloro-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridin 5 yl]-6- sopropyl 1H pyridin 2-one (250mg) with triflic anhydride (0 14mL) in the presence of triethyl amine (0 17mL) gives, after purificat on on silica gel trifluoro-methanesulfonic ac d 3 [6-chloro-1-((S)-2 methoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid n-5-yl]-6-isopropyl-pyridin-2 yl ester LCMS m/z 506 1/508 1 (M+H) Rt = 4 02 mins

Step L

Analogo s to th preparation of 5-(2-ethyl-6-isopropyl-pyrid n 3 yl)-6-methoxy 1-((S)-2 methoxy 1-methyl-ethyl) 3 methyl 1H-pyrrolo[3 2-b]pyridine, reaction of trifluoro-methanesulfonic ac d 3 [6-chloro-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid n 5 yl] 6-isopropyl-pyrid n 2 yl ester (145mg) with triethylborane solut on n hexanes (1 2mL, 1 0M) affords, after purif cation on s lica gel 6-chloro-5-(2 ethyl 6-isopropyl pyridin 3 yl)-1 ((S)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridi LCMS m/z 386 2/388 2 (M+H) Rt = 2 02 mins Isolated as a byproduct of this

reaction is 6-chloro-5-(6-isopropyl pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2-b]pyridine LCMS m/z 358.2/360.2 (M+H) Rt = 2 15 mins

Step M

Analogous to th preparation of ethyl {6-isopropyl 3 [6-methoxy-1-((S)-2 methoxy-1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridin 5 yl]-pyridin 2 yl}-amine the reaction of tr fluoro-methanesulfon ac d 3 [6-chloro-1-((S)-2 methoxy-1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin-5 yl]-6-isopropyl-pyridin-2 yl ester (85mg) with methyl amine solution i THF (0 9mL 2M) gives, after purification on silica gel {3-[6-chloro-1-((S)-2-methoxy-1 methyl-ethyl)-3-methyl 1H pyrrolo[3,2 b]pyridin-5-yl]-6-isopropyl pyridin 2 yl}-methyl amin LCMS m/z 387.2/389 2 (M+H) Rt = 2 09 mins

Replacing the amine in step M of Example 35 with various other amine reagents the following compounds are synthesized

{3 [6-Chloro-1-(2 methoxy-1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl] 6 isopropyl pyridin 2 yl}-dimethyl-amine Rt 2 12min m/z 401.2(M+H)

{3 [6-Chloro-1-(2 methoxy 1 methyl-ethyl)-3-methyl-1H pyrrolo[3,2 b]pyridin 5 yl]-6- sopropyl-pyridin 2 yl}-ethyl-amine Rt 2.22min m/z 401 2(M+H)

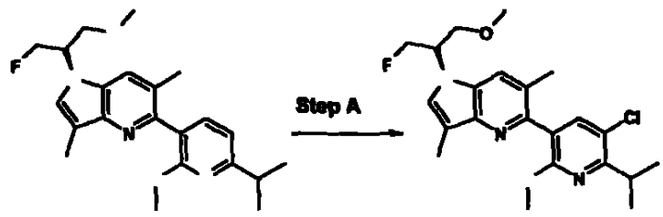
EXAMPLE 36

Sy thesis of {3-[6-chl ro-1-((R)-1 flu romethyl-2-methoxy-ethyl)-3-methyl-1H pyrrol [3,2-b]pyrid n 5-yl] 6-isopropyl-pyridin 2 yl} m thyl-am ne nd 6-chloro-5-(2 ethyl-6-isopropyl-pyridin-3-yl)-1-((R)-1 fluoromethyl-2-meth xy-ethyl)-3-methyl-1H pyrrolo[3,2-b]pyridine

Substituting (R)-1-(tert Butyl-dimethyl-silanyloxymethyl)-2-methoxy-ethylamine for (S)-1 methoxy-2-propylamine in the scheme of Example 35 and introducing the fluoro group after step F as described in steps F and G of Example 13 gives {3 [6-chloro-1-((R)-1 fluoromethyl 2 methoxy-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl] 6-isopropyl pyridin 2 yl} methyl-amine, Rt 2 09min m/z 405.2(M+H) and 6-chloro-5-(2-ethyl-6-isopropyl pyrid n-3 yl)-1-((R)-1 fluoromethyl-2 methoxy-ethyl)-3-methyl 1H pyrrolo[3,2 b]py din Rt 2 34min m/z 448 12(M+H)

EXAMPLE 37

Synthesis of {5-Chloro-3-[1-((R)-1 fl romethyl-2-methoxy-ethyl)-3,6-d methyl-1H pyrrol [3,2-b]pyrid 5-yl] 6-isopropyl-pyrid n 2-yl} methyl- m

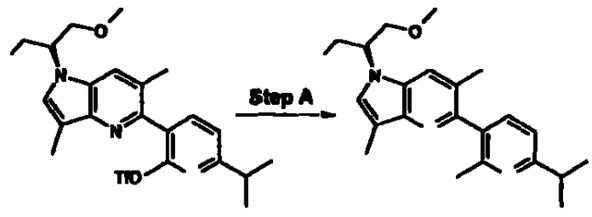


Step A

N-Chlorosuccinimide (33mg) is added to a solution of {3 [1-(1 fluoromethyl 2 methoxy ethyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin-2 yl}-methyl-am e (94mg) in chloroform (3mL) After 18 h additional N-chlorosuccin mide (10mg) is added and then fter further 5 min water (10mL) and dichloromethane (10mL) are added to the reaction mixture. The organ layer is separated dried and evaporated to give, after chromatography over silica gel {5-Chloro-3 [1-((R)-1 fluoromethyl 2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl-pyridin 2 yl} methyl-amine Rt 2 67min m/z 419 2(M+H)

EXAMPLE 38

Sy thesis of 1-((R)-1-fluoromethyl-2-methoxy ethyl)-5-(6-isopropyl-2 methyl-pyridin-3-yl)-3,6-d methyl-1H py rolo[3,2-b]pyridin



Step A

Trifluoro-methan sulfonic acid 3 [1-(1 fluoromethyl 2-methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyridin-5 yl]-6-isopropyl pyrid 2 yl ester (97mg) bis(triphenylphosphi e)palladium(II) hlor de (4mg) nd lithium chloride (25 mg) are introduced in a glass t ibe that was then filled with nitrogen DMF (2mL) and tetramethyltin (30uL) are added, the tube is closed with a cap and the reaction mixture is heated at 100°C overn ght Water (2mL) and EtOAc (2mL) are added and then the organic layer is separated

The aqueous layer is extracted three more times with EtOAc and then the combined organic phase is dried and evaporated to give after silica gel purification 5-((R)-1 Fluoromethyl 2 methoxy-ethyl)-5-(6-isopropyl 2 methyl-pyridin-3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine Rt 1 83min m/z 370.2(M+H)

EXAMPLE 39

In manner analogous to the synthesis of 1-((R)-1 fluoromethyl 2 methoxy-ethyl) 5-(6-isopropyl 2 methyl pyridin-3 yl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine, trifluoro-methanesulfonic acid 3 [6-chloro-1-((S)-2-methoxy-1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2-b]pyridin 5 yl]-6 isopropyl pyridin-2 yl ester affords 6-chloro-1-((R)-1 fluoro-methyl 2-methoxy-ethyl)-5-(6-isopropyl 2-methyl pyridin-3 yl)-3-methyl 1H-pyrrolo[3,2-b]pyridine Rt 2 17min m/z 390 11(M+H)

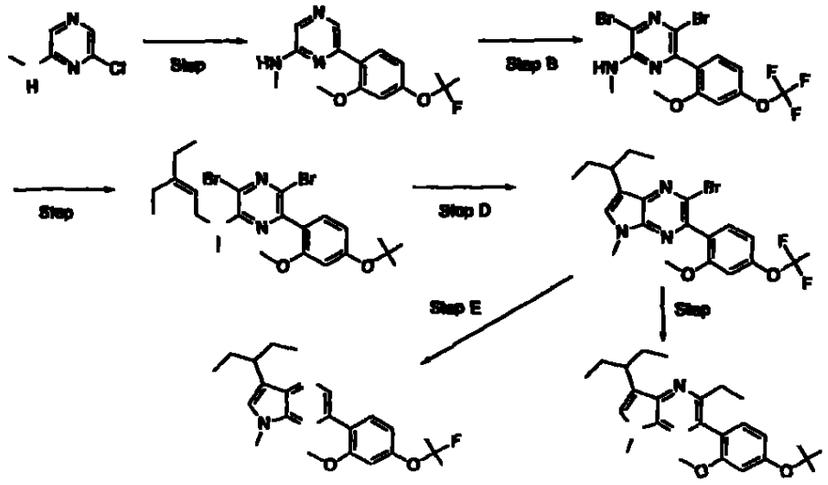
EXAMPLE 40

Synthesis of Ethyl-{3-[1-((R)-1 fluoromethyl-2-methoxy-ethyl)-3,6-dimethyl-1H pyrrolo[3,2 b]pyridin 5-yl]-6-isopropyl-pyrid n-2-yl}-amin

In a manner analogous to the synthesis of {3 [1-((R)-1 Fluoromethyl-2 methoxy-ethyl)-3 6-d methyl 1H pyrrol [3,2 b]pyridin 5 yl]-6-isopropyl-pyr din 2 yl} methyl-amine trifluoro-methanesulfonic acid 3 [1-(1 fluoromethyl 2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl-pyridin-2-yl ester and ethylamine afford ethyl-{3 [1-((R)-1 fluoromethyl-2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridin-5 yl]-6- sopropyl pyridin-2 yl}-amine Rt 2 03min m/z 399.2(M+H)

EXAMPLE 41

Synthesis f 2-bromo-7-(1-ethyl-propyl)-3-(2-methoxy-4-trifluo omethoxy phenyl)-5-methyl-5H pyrrolo[2,3-b]pyrazine, 7-(1-ethyl-propyl)-3-(2-methoxy-4 trifl oromethoxy phenyl)-5-methyl 5H pyrrol [2,3-b]pyrazine and 2 ethyl-7-(1 ethyl-propyl)-3-(2-methoxy-4-trifluoromethoxy phenyl)-5-methyl-5H pyrrolo[2,3-b]pyrazine



Step A

A mixture of (6-chloro-pyrazin 2 yl)-methyl-amine (431 mg, 3 mmol), 2 methoxy-4 trifluoromethoxyphenyl boronic acid (780 mg, 3 3 mmol) in 2M Na_2CO_3 (3 mL, 6 mmol) and toluene (3 mL) s treated with $Pd(PPh_3)_4$ (50 mg) under nitrogen t 80 C f r 16 h After cooling to room temperatu re, the product is extracted with ethyl acetate (3 x 10 mL), dried concentrated and purified by silica gel column hromatography to give[6-(2-methoxy-4-trifluoromethoxy-phenyl)-pyrazin 2 yl] methyl-amine LC MS (M + 1) 300

Step B

To a sol tion of [6 (2 methoxy-4 trifluoromethoxy phenyl)-pyrazin 2 yl] methyl-am ne (1 2 g, 4 mmol) in chloroform (20 mL) is added NBS (1 78 g, 10 mm l) in one portion t 0 C The mixture is then stirred at room temperature for 15 min followed by concentration and purification by silica gel column chromatography to provide [3 5-dibromo-6-(2 methoxy-4 trifluoromethoxy phenyl) pyraz n 2 yl] methyl-ami e LC-MS (M + 1) 458

Step C

To a solution of NaH (95%, 65 mg, 4.5 mmol) and Bu_4NBr (144 mg, 0.45 mmol) in anhydrous NMP (2 mL) is added dropwise a solution of [3,5-dibromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-pyrazin-2-yl]-methyl-amine (1.37 g, 3 mmol) in NMP (10 mL) under nitrogen at room temperature in 5 min. The mixture is continued stirring at room temperature for 1 h, followed by addition of 1-chloro-3-ethyl-pent-2-ene (594 mg, 4.5 mmol). The mixture is then heated at 65 °C for 16 h. After cooling to room temperature, the product is extracted with ethyl acetate (3 x 20 mL), washed with water (2 x 8 mL) and brine (10 mL), dried, concentrated and purified by silica gel column chromatography to give [3,5-dibromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-pyrazin-2-yl]-(3-ethyl-pent-2-enyl)-methyl-amine.

Step D

A mixture of [3,5-dibromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-pyrazin-2-yl]-(3-ethyl-pent-2-enyl)-methyl-amine (1.77 g, 3.2 mmol), Bu_4NBr (1.02 g, 3.2 mmol), K_2CO_3 (1.33 g, 9.6 mmol) and $Pd(OAc)_2$ in anhydrous DMF (20 mL) under nitrogen is heated at 90 °C for 1 h. After cooling to room temperature, the reaction is quenched by addition of water (10 mL). The product is extracted with ethyl acetate (3 x 20 mL), washed with water (2 x 8 mL) and brine (10 mL), dried, concentrated and purified by silica gel column chromatography to give 2-bromo-7-(1-ethyl-propyl)-3-(2-methoxy-4-trifluoromethoxy-phenyl)-5-methyl-5H-pyrrolo[2,3-b]pyrazine. LC-MS (M + 1): 472.

Step E

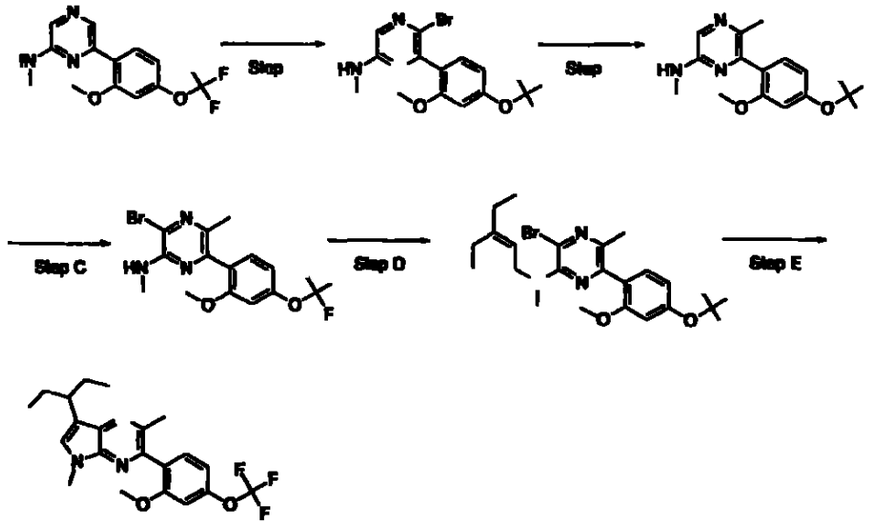
A solution of 2-bromo-7-(1-ethyl-propyl)-3-(2-methoxy-4-trifluoromethoxy-phenyl)-5-methyl-5H-pyrrolo[2,3-b]pyrazine (50 mg, 0.106 mmol) in ethyl acetate (5 mL) is hydrogenated with 5% Pd-C (10 mg) under atmosphere at room temperature overnight. After filtration and concentration, the product is purified by silica gel column chromatography to give 7-(1-ethyl-propyl)-3-(2-methoxy-4-trifluoromethoxy-phenyl)-5-methyl-5H-pyrrolo[2,3-b]pyrazine. ^1H NMR ($CDCl_3$, δ): 0.85 (t, J = 7.2 Hz, 6H), 1.82 (m, 4H), 2.87 (m, 1H), 3.87 (s, 1H), 3.88 (s, 3H), 6.86 (s, 1H), 6.98 (d, J = 8.4 Hz), 7.19 (s, 1H), 7.87 (, d, J = 8.4 Hz, 1H), 8.90 (s, 1H). LC MS (M + 1): 394.

Step F

A mixture of 2-bromo-7-(1-ethyl-propyl)-3-(2 methoxy-4-trifluoromethoxy-phenyl)-5 methyl 5H pyrrolo[2,3-b]pyraz (47 mg, 0 1 mmol) Et_3B (1M solution in hexane, 0 2 mL, 0 2 mmol) in 2M Na_2CO_3 (0 5 mL, 1 mmol) and toluene (1 mL) is treated with $Pd(PPh_3)_4$ (10 mg) under nitrogen at 90 °C for 16 h After cooling to room temperature, the product s extracted with ethyl acetate (3 x 10 mL), dried concentrated and purified by silica gel column chromatography to give 2-ethyl 7-(1-ethyl propyl)-3-(2 methoxy-4 trifluoromethoxy-phenyl)-5 methyl 5H pyrrolo[2 3-b]pyrazine ^{1}H NMR ($CDCl_3$, δ) 0 87 (t J= 7 6 Hz, 6H), 1 17 (t, J = 7 6 Hz, 3H), 1 82 (m 4H), 2 69 (m 2H) 2 92 (m 1H), 3 77 (s, 1H), 3 81 (s, 3H), 6 83 (s 1H), 6 94 (d J= 8 0 Hz), 7 12 (s, 1H), 7 31 (d J= 8 0 Hz, 1H), LC-MS (M + 1) 408

EXAMPLE 42

Synthesis of 2-methyl-7-(1-ethyl propyl)-3-(2-methoxy-4-trifl oromethoxy phenyl)-5-methyl-5H pyrrolo[2,3-b]pyrazine



Step A

To a sol tion of [6-(2 methoxy-4 trifluoromethoxy phenyl)-pyrazi 2 yl] methyl-amine (3 g, 10 mmol) in chloroform (25 mL) is added NBS (2 13 g, 12 mmol) in one portion at 0 °C The mixture is then stirred at room temperature for 30 mi followed by concentration and purification by s lica gel column chromatography to provide [5-bromo-6-(2 methoxy-4-trifluoromethoxy phenyl)-pyrazin 2 yl] methyl-am ne LC-MS (M + 1) 378

Step B

A mixture of [5-bromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-pyrazin-2 yl]-methyl-amine (120 mg, 0 32 mmol), $MeB(OH)_2$ (192 mm 3.2 mmol) in 2M Na_2CO_3 (2 mL, 4 mmol) and toluene (2 mL) is treated with $Pd(PPh_3)_4$ (20 mg) under nitrogen at 85 C for 16 h After cooling to room temperature, the product is extracted with ethyl acetate (3 x 10 mL), dried, concentrated and purified by silica gel column chromatography to give [6-(2 methoxy-4-trifluoromethoxy phenyl)-5-methyl pyrazin 2 yl] methyl-amine

Step C

[3-bromo-6-(2-methoxy-4-trifluoromethoxy-phenyl)-5 methyl pyrazin-2 yl]-methyl-amine is prepared by the same procedure as described in step A LC-MS 392

Step D

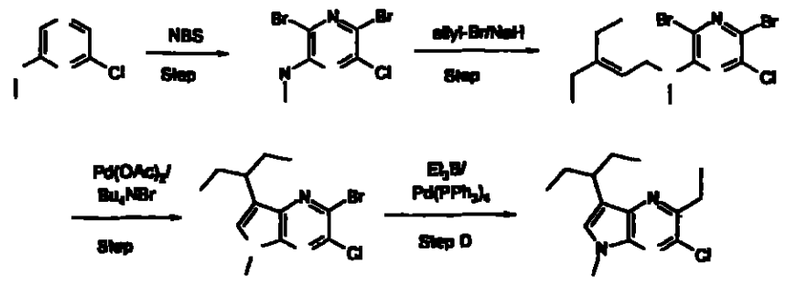
[3 bromo-6-(2 methoxy-4-trifluoromethoxy phenyl)-5 methyl pyrazin 2 yl]-(3-ethyl pent 2 enyl)-methyl-amine is prepared by the sam procedure for [3 5-dibromo-6 (2-methoxy-4-trifluoromethoxy-phenyl)-pyrazin-2 yl]-(3-ethyl pent 2-enyl)-methyl-amine

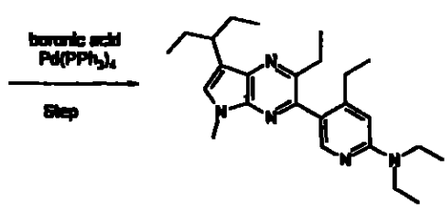
Step E

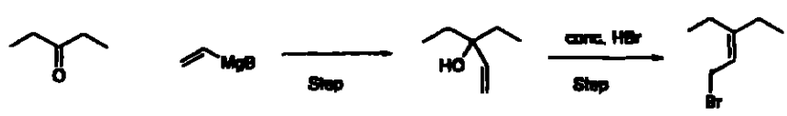
7-(1 Ethyl propyl)-3-(2 methoxy-4-trifluoromethoxy phenyl)-2 5-dimethyl 5H pyrrolo[2,3 b]pyrazine is prepared by the same proced re for 2 bromo-7-(1-ethyl propyl)-3-(2 n ethoxy-4-tr fluoromethoxy-phenyl)-5 methyl 5H pyrrolo[2 3 b]pyrazine H NMR ($CDCl_3$, δ) 0 86 (t, J = 7 6 Hz, 6H) 1 83 (m 4H) 2 42 (s, 3H) 2 93 (m 1H), 3 78 (s, 1H) 3 81 (s, 3H) 6 83 (s, 1H) 6 94 (d J = 8 0 Hz), 7 12 (s, 1H) 7 31 (d, J = 8 0 Hz, 1H) LC-MS (M + 1) 422

EXAMPLE 43

Synthesis of N,N-diethyl-{4-ethyl-5-[2-ethyl 7-(1-ethyl-propyl)-5-methyl-5H pyrrolo[2,3-b]pyrazin-3-yl] pyridin 2-yl} ami







St p A

Th pre iously described 2-chloro-4 methyl minopyra (40 0g) is d ssolved i hloroform (500mL) and NBS (104 0g) is added Afte he ng stirred for 16h, the yellow sh mixture is put i to wate (500mL) and sat. sod um bicarbonate (100mL) extra ted with ethyl acetate/hexane (1/3 2x400mL) and dried over m gnesium sulfate The crud s then flushed through a plug of sil ca gel (ethyl acetate/hexane = 1/3) and used without any other purification TLC Rf = 0 63 (ethyl acetate/hex = 1/3)

Step B

The crude dibrom de (73 69g) of step A and the later described 3-d ethyl llyl bromide (84 40g, step F +G) are d ssolved DMF (400mL) Sod m hydride (15 50g) is added n portions and the reaction is stirred for 30 min at rt The mixture is then put nto water (2000mL) a d xtracted w th ethyl acetate/hex (1/6 4x700mL) The comb ed orga c layers are washed with water (200mL), dried over mag esium sulfate and filtered directly

through a plug of silica gel (200g) The crude material is used directly in step C TLC Rf = 0 90 (EtOAc/hex = 1/6)

Step C

The crude allyl compound (116 0g) of step B tetrabutylammonium bromide (75 3g) palladium acetate (5.2g), and potassium carbonate (97 0g) are dissolved in DMF (1200mL) After being heated to 80 °C for 6h, the mixture is worked up according to step B Final purification on silica gel affords the bicyclic compound TLC Rf = 0 59 (EtOAc/hex = 1/6)

Step D

The bicyclic compound (1 83g) of step C is dissolved in toluene (50mL) After degassing, tetrakis(triphenylphosph ne)palladium (0) (0 67g) is added A second degassing is followed by addition of triethylborane (28 9mL, 1N in hexane) and of a 2N potassium carbonate solution (6 0mL) where pon the reaction s heated to 80 °C for 36h The yellowish mixture s then put nto water (200mL) extracted with DCM (3x150 mL) and dried over magnes um sulfate Purif cat on o sil ca g l affords the ethyl de v ati LCMS m/z 266 14 (M+H)

Step E

Th ethyl deri tive (500mg) of step D and the previously described 2-d ethylamino-4-ethyl 5 pyr dine boron ac d (526mg) are dissolved in DME (15mL) After degassing, tetrakis(tr phenylphosph ne)palladium (0) (183mg) is added A seco d degassing is followed by addition of a 1N sod um carbonate solution (3.2mL) whereupon the reaction is heated to 80 °C for 40h The yellowish mixture is then put into water (100mL) extracted with DCM (3x100mL), and dried over magnesium sulfate Purification on sil ca gel affords the title compo nd LCMS m/z 408 37 (M+H)

Step F

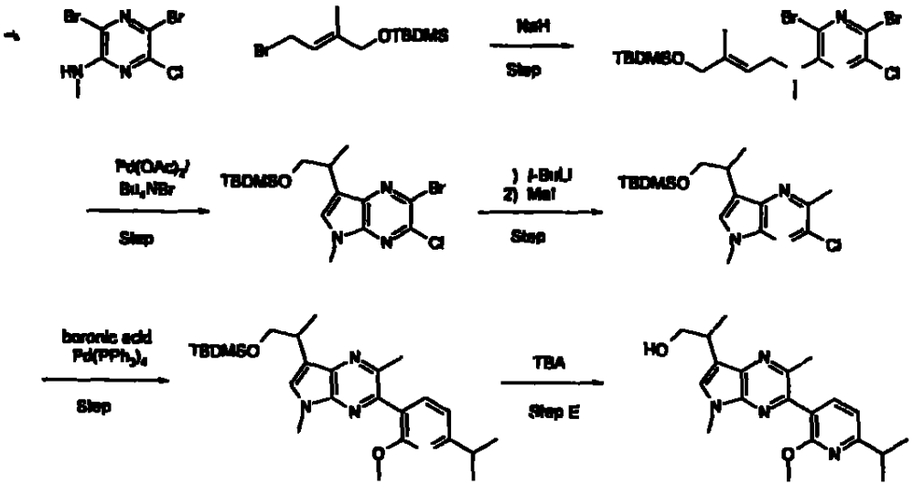
3 Pentanone (73 9mL) in THF (300mL) s slowly added to v nyl magnes um bromide (800mL, 1N in THF) t rt. After being stirred for 24h, the mixture is put into water (2500mL) and sat sodium bicarbonate (500mL) extracted with DCM (1x1500mL 2x500mL) and dried o er magnesium sulfate The rude mixture is used without any further purification in step G

St p G

The crude mixture (82 0g) of step F is dissolved in conc HBr (250mL) After 20 m or o ce NMR control shows completed conversion the dark mixture is put into water (500mL) extracted with DCM (3x250mL), and dried over magnes um sulfate The crude mixture s used without any further purification in step B

EXAMPLE 44

Synthes s of 2 [3-(6- sopropyl-2 methoxy pyridin-3 yl)-2,5-dimethyl 5H pyrrolo[2,3-b]pyrazin-7 yl] propan 1-ol



Step A

The previo sly desc ibed 2 6-d bromo-3-chloro-5 methylaminopyraz ne (550mg) a d the shown allylic bromide (560mg synthesized identically to the Me-regio somere described by Enders *t al* Synlett 2002, 2280) are dissolved in DMF (10mL) Afte add tio of sod m hydride (91mg) the dark red reaction mixture is stirred fo 15 min S bseq ently th mixture s put into water (200mL) and sat sodium bicarbonate (100ml) extracted with ethyl ether (2x100mL) and dried ove magnesium sulf te Purification on silica gel affords the allylic compound TLC Rf = 0 69 (EtOAc/hex = 1/6)

Step B

The allylic compound (892mg) of step A tetrabutylammonium bromide (575mg) palladium acetate (40mg) and potass um carbonate (737mg) are dissolved in DMF (10mL) Afte

heating to 80 °C for 30 min the mixture is worked-up according to step A Purification on l ca g l affords th Heck product LCMS m/z 417 93 (M+H)

Step C

The Heck product (356mg) of step B is dissolved in THF (2 5mL) and added to a solution of *t* BuLi (1 05mL 1 7N in pentane) in THF (8 5mL) at 78 °C After being stirred for 10 min, methyl iodide (0.21mL) s added and the reaction mixture is st rred for another 1h at 78 °C Subsequently the mixture is put into water (100mL) and sat sodium bicarbonate (50ml) xtracted with DCM (3x100mL), and dried over magnesium sulfate Purification on silica gel affords the methyl derivative LCMS m/z 354 12 (M+H)

St p D

Th methyl product of step C (238mg) and th prev ously described 2 *iso*propyl-6-methoxy 5 py din boron ac d (158mg) are dissolved in DME (5 0mL) After degassing, tetrakis(triphenylphosphine)palladium (0) (77mg) is added A second degassing is followed by add t on of a 1N sodium carbonate solution (1 35mL) whereupon the reaction is heated to 80 °C for 3h The yellow sh mixture is then put into water (100mL) extracted with DCM (3x100 L), and dried over magnesium sulfate P rification on sil ca g l affords the coupled prod ct LCMS m/z 469 15 (M+H)

St p E

The Suzuki product of step D s dissol ed in THF (5 0mL) After addition of TBAF monohydrate (650mg) the reaction m xture is stirred for 30 min Subsequently the yellow solutio is p t into water (100mL) xtracted with DCM (3x100mL) and dried over magnesium sulfate Purification on silica gel affords the title compound LCMS m/z 355 16 (M+H)

EXAMPLE 45

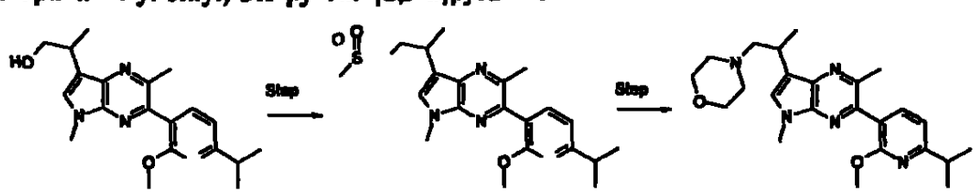
Synthesis of 3-(6-isopropyl 2 methoxy pyridi -3-yl)-7-(2 methoxy 1 methyl-ethyl)-2,5-d methyl-5H pyrrolo[2,3 b]pyraz e



2 [3-(6 Isopropyl 2-methoxy pyrid n 3 yl)-2 5-dimethyl 5H-pyrrolo[2 3 b]pyraz n 7 yl] propa 1-ol (33mg) is dissolved in THF (5 0mL) After addition of sodium hydride (74mg), the loudy mixture s stirred for 5min before methyl od de (0 23mL) is added The reaction is stirred for 16h put into w te (100mL) and sat sodi m b carbon te (10ml), extracted with DCM (3x100mL) and dried o er magnesi m sulfate Pi rif cation o il ca gel afford th title compound LCMS m/z 369 15 (M+H)

EXAMPLE 46

Synthesis of 3-(6-isopropyl-2-methoxy pyridin 3-yl)-2,5-dimethyl-7-(1 methyl 2-m rph li -4-yl-ethyl)-5H py rol [2,3-b]pyra e



Step A

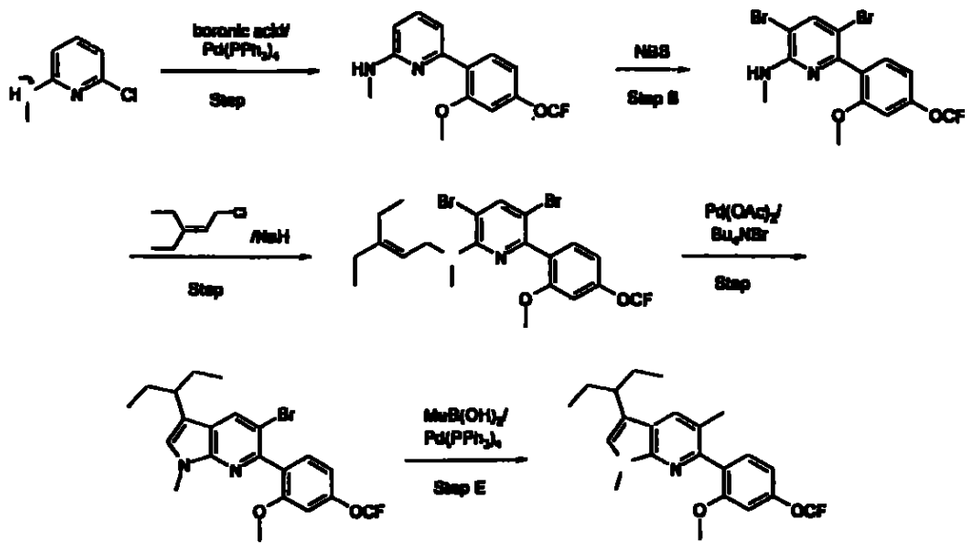
2 [3-(6 Isopropyl 2 methoxy pyridin 3 yl)-2 5-dimethyl 5H pyrrolo[2 3 b]pyrazin 7 yl] propa 1-ol (142mg) s dissol ed in DCM (5 0mL) and cooled to 0 °C Mesyl chloride (34µL) and triethylamine (78µL) are added before the react on is stirred fo 30 min at 0 °C Subsequently the yellow solution is put into water (100mL) extracted with DCM (3x100mL) nd d ied o c magnes um sulfate The crude m xture s carried on to step B witho t ny furthe p rification LCMS m/z 433 07 (M+H)

Step B

The mesylate (54mg) of step A is dissolved in acetonitrile (1.0mL). After addition of morpholine (200mg) the reaction is heated to 80 °C for 3h. Subsequently the clear solution is put into water (100mL) extracted with DCM (3x100mL), and dried over magnesium sulfate. Purification on silica gel affords the title compound. LCMS: m/z 424.13 (M+H)

EXAMPLE 47

Synthesis of 3-(1-ethyl-propyl)-6-(2-methoxy-4-trifluoromethoxy-phenyl)-1,5-dimethyl-1H-pyrrolo[2,3-b]pyridine



Step A

The previously described 2-chloro-6-methylaminopyridine (670mg), the also previously described 2-methoxy-4-trifluoromethoxyphenyl boronic acid (1.37g), and $Pd(PPh_3)_4$ (115mg) are dissolved in toluene (30mL). After addition of 2N Na_2CO_3 (6mL), the mixture is degassed and then heated at 85 °C overnight. The solution is diluted with EtOAc and washed with 2N NaOH, H_2O, brine and dried over $MgSO_4$. Purification on silica gel yields the Suzuki product. ^1H NMR ($CDCl_3$, δ ppm): 7.78 (1H, d, J = 8.4 Hz), 7.49 (1H, t, J = 7.6 Hz), 7.08 (1H, d, J = 7.6 Hz), 6.90 (1H, dd, J = 7.4, 2.0Hz), 6.80 (1H, d, J = 2.0Hz), 6.34 (1H, J = 8.4Hz), 4.66 (1H, brs), 3.84 (3H, s), 2.94 (3H, d, J = 5.0Hz)

Step B

To cooled solution of the Suzuki product from Step A (1.0g) in $CHCl_3$ is added a solution of NBS (1.22 g) in $CHCl_3$ at 0 °C over 30 min. After heating at reflux for 1h the reaction

mixture ev porated The res due then purif ed on l ca gel to y eld the brom de H NMR ($CDCl_3$, δ ppm) 7 80 (1H s) 7 28 (1H d J= 8 4 Hz) 6 90 (1H dd, J= 8 4 1 1Hz) 6 79 (1H), 5 03 (1H brs) 3 82 (3H) 2 98 (3H d J= 5 0Hz)

Step C

To a sol tion of the crude bromide (1 1g) from step B n NMP (10mL) is added NaH (60% 0 195g) Afte be g st rred for 2h freshly dist lled 3 3-d ethyl llyl chlorid (0 414g, prepared analogously to the previously described 3 3-diethyl llyl bromide) is added to the reaction mixture St rring for an additional 1h is followed by quenching with H_2O and extraction with EtOAc The organic layer is washed with H_2O brine, and dried over Na_2SO Purification on silica gel yields the allyl compound ^1H NMR ($CDCl_3$ δ ppm) 7 95 (1H s) 7 28 (1H d J= 8 3 Hz), 6 90 (1H d J= 8 3Hz) 6 79 (1H s), 5 30 (1H m) 3 92 (2H d J= 6 6Hz), 3 81 (3H s), 2 87 (3H) 2 06 (4H m), 1 01 (3H t, J= 7 5Hz), 0 94 (3H t, J= 7 5Hz)

Step D

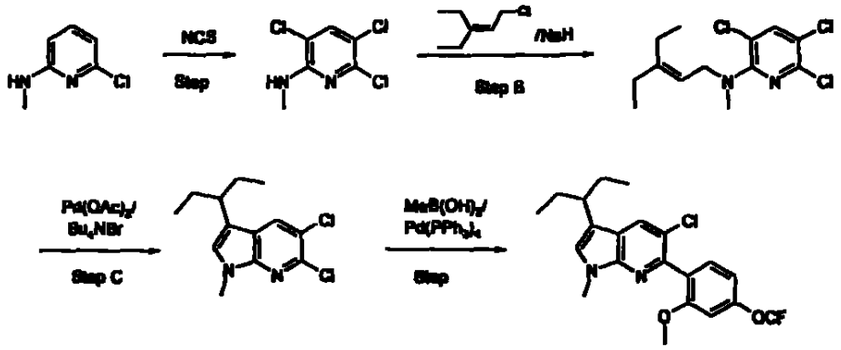
The allyl compo nd of step C (330mg), $Pd(OAc)_2$ (40mg), tetrabutylammoni m brom de (219mg) a d K_2CO (250mg) are d ssolved n DMF (3mL), degassed a d heated to 80 C overnight Th mixture is then d l ted w th EtOAc nd washed with H O b ne, a d dried over $MgSO_4$ Purification on s lica gel yields the Heck product ^1H NMR ($CDCl_3$ δ ppm) 8 11 (1H s) 7 31 (1H d J= 8 3 Hz) 6 94 (2H, m), 6 82 (1H, d J= 1 7 Hz) 3 81 (3H s),3 80 (3H s) 2 58 (1H m) 1 62 1 79 (4H m), 0 85 (6H t, J= 7 3Hz)

Step E

The Heck product of step D (80mg), methylboron c ac d (60mg), a d $Pd(PPh_3)_4$ (10mg) are dissolved in toluene (5mL) After addition of 2N Na_2CO_3 (3mL) the reaction mixture is d gassed a d then heated to 85 °C overnight Subseq ently th sol tio s d luted w th EtOAc and washed with 2N N OH H O and bri e before bei g dried ove MgSO Purification o silica gel y elds the title compou d H NMR ($CDCl_3$ δ ppm) 7 73 (1H) 7 32 (1H d J= 8 2 Hz), 6 93 (1H d J= 8 2 Hz) 6 88 (1H s) 6 82 (1H s) 3 81 (3H s) 3 78 (3H s), 2 18 (3H, s) 1 68 1 79 (4H m) 0 86 (6H t, J= 7 3Hz)

EXAMPLE 48

Synthesis of 5-chloro-3-(1-ethyl-propyl)-6-(2-methoxy-4-trifluoromethoxy-phenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine



Step A

NCS (2.95g) is added to a solution of the previously described 2-chloro-6-methylaminopyridine (1.43g) in acetonitrile (40mL) whereupon the reaction mixture is heated to 70 °C for 48h. Subsequently the yellow solution is diluted with EtOAc, washed with H_2O, brine and dried over Na_2SO_4. Purification on silica gel yields the trichloride. ^1H NMR (CDCl$_3$, δ ppm) 7.50 (1H, s), 5.07 (1H, brs), 3.04 (3H, d, J = 5.0Hz).

Step B

To a solution of the trichloride from step A (1.03g) in NMP (20mL) is added tetrabutylammonium bromide (0.2g) and NaH (60%, 0.38g). After being stirred at rt for 3h, 3,3-diethylallyl chloride (0.97g, prepared analogously to the previously described 3,3-diethylallyl bromide) is added and the reaction mixture is stirred for an additional 36h. The yellow solution is then quenched with water and extracted with EtOAc. The organic layer is washed with water, brine, and dried over $MgSO_4$ to yield the crude allylamine which was used in step C without any further purification. H NMR (CDCl$_3$, δ ppm) 7.58 (1H, s), 5.23 (1H, t, J = 6.7Hz), 3.96 (2H, d, J = 6.7Hz), 2.92 (3H, s), 2.05-2.09 (4H, m), 0.94-1.00(6H, m).

Step C

The allyl compound of step B (100mg), $Pd(OAc)_2$ (10mg), TBAB (116mg), and K_2CO_3 (132mg) are dissolved in DMF (2mL), degassed and heated to 80 °C overnight. The mixture

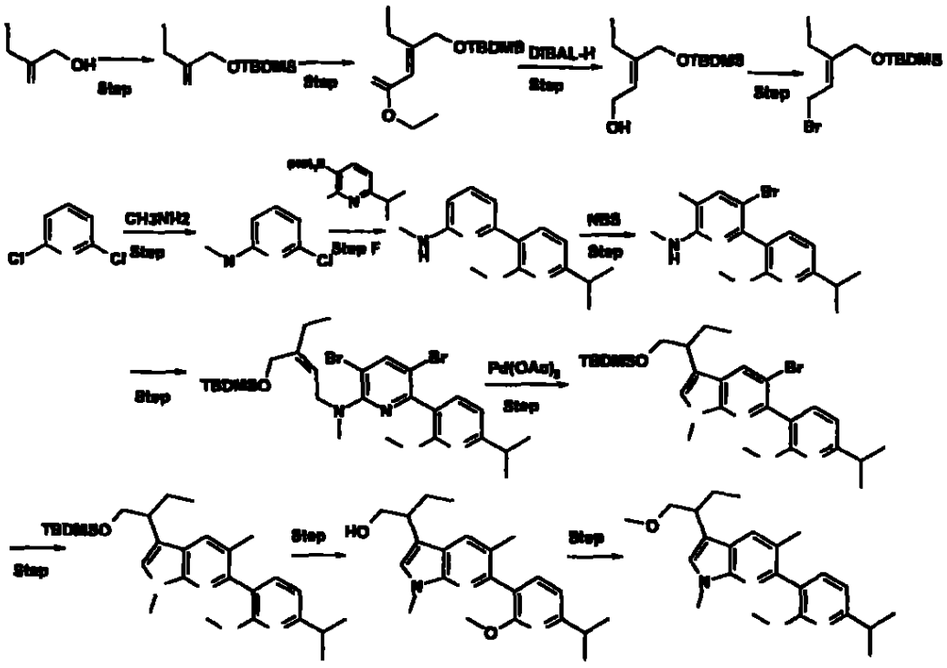
is then diluted with EtOAc a d washed w th H_2O brine and dried over MgSO Purificat on on silica gel yields the Heck product.

Step D

The Heck product of step C the pre iously described 2 methoxy-4-trifluoromethoxyphenyl boronic acid a d $Pd(PPh_3)_4$ are dissolved in toluene After addition of a 2N Na_2CO_3, the reaction mixture is degassed and then heated to 85 °C overn ght. Subsequently the solution is diluted with EtOAc nd washed with 2N NaOH H_2O nd brine before be g dried over MgSO Purification on s lica gel yield the title compo nd ^{1}H NMR ($CDCl_3$ δ ppm) 7 73 (1H s), 7 39 (1H d J= 8 2 Hz), 6 95 (1H s) 6 93 (1H d J= 8 2 Hz) 6 82 (1H s) 3 81 (6H brs), 2 59 (1H m), 1 68 1 79 (4H m) 0 84 (6H t, J= 7 3Hz)

EXAMPLE 49

Synthesis f 6-(6-Isop pyl-2-m th xy pyrid 3 yl)-3-(1 meth xym thyl-propyl)-1,5-d m thyl 1H py rol [2,3-b]pyrid



Step A

TBDMSCl (20g) is added to cold (0°C) solution of 4 hydroxy 2 b tano (17 6g) DMAP (200mg), imidazole (10 8g) in DMF (160ml) The reaction m xture is warmaed naturally to

room temperature and stirred for 24 hours The reaction mixture is added w th water and extracted with ethyl acetate and dried with Na_2SO_4 Purification by column with hexane/ethyl acetate gives product. Rf 0 4(hexane/ethyl acetate 8 1)

St p B

Triethyl phosphonoacetate (17 3ml) is added as a solution of THF (30ml) to cold (0°C) suspension of NaH (0 131mol) in anhydrous THF (80ml) The resulting mixture is stirred at 0°C for 1 hour before ketone (17 67g) is added as a solution of THF (10ml) The reaction is continued at room temperature for another 2 hours. Saturated aqueous NH_4Cl is carefully added and separated Aqueous lay r s extracted with ether The combined organic layers are washed with water br ne Purification by column with hexane/ethyl acetate gives product Rf 0 4(hexane/ethyl acetate 15 1)

Step C

Starting material (21 3g) s treated w th DIBAL H(1 0M n toluene 196ml) at 0°C for 6 hours Wate s carefully added to quench the excess DIBAL The reactio mixture is filtered and washed with ethyl acetate The f ltrate is conce trated to afford the rude product. Rf 0 4(hexane/ethyl acetate 3 1)

Step D

Start ng ate ial (8 75g) is take n anhydrous methylene chloride (110ml) triethylamine is added The res lting m xture ooled to -40°C MsCl s added dropw se and the react on s continued for 1 hour at -40°C before LiB (13.2g) is added as sol tion of THF (120ml) The resulting react on mixture is warmed naturally to room temperature and continued for another 1 hour The reaction is quenched with water and separated Aqueous layer is extracted with ether The combined organic l yers are washed with brine and dried with Na_2SO_4 The crude product can be used for the next step reactio without further pur fication Rf 0 4(hexane/ethyl acetate 20 1)

Step E

2 6-dichloropyr dine (17g) and CH_3NH_2 aqueous sol tion (40%, 26 8g) are taken in THF (100ml) se led tube and s heated at 80°C for 24 ho rs The reaction is ooled to room temperature and dil ted with water The resulting mixture is separated and extracted w th

ethyl acetate The comb ned orga c layers re washed with brine and dried with Na_2SO The crude product s used for the next step reaction without further purification LCMS 143 3 (M+H)

Step F

A mixt re of 2-chloro-6-methylamino-pyrid ne (3 56 0 025mol)) 2 methoxy-6 isopropyl 3 pyr dylboron c ac d (6 33g), $Pd(PPh_3)_4$ (577mg) aqueous Na_2CO_3 sol t on (1 0M 50ml) and toluene (50ml) is heated overnight at 100°C under a dinitrogen atmosphere The reaction mixture is cooled to room temperature and separated The aqueous layer is extracted with ethyl acetate The comb ed orga c layers are washed with brine and dried with Na_2SO Th crude product i used for th ext step reaction with t further p f cat on Rf 0 4(hexane/ethyl acetate 4 1)

Step G

The crude start g m ter l tak hydrous CHCl (100ml) 4 0 eq lent of NBS added in one portion at 0°C The reaction is complete in 0 5 ho The react on mixture s wa hed w th water nd d d w th N_2SO Pu f cat o by flash column w th hexane/ethyl acetate gi es product as clear o l LCMS m/z 496 1 (M+H)

Step H

NaH (795mg, 60% i m neral o l) s added to a solutio of starting m ten l (6 34g) n anhydrous DMF (100ml) and st rred at room temperature for 10m n te Brom d (4 93g) prepared n Step D is added dropw se and the res lting mixture s stirred for 3 hours The reaction m xture s carefully quen hed w th wate The result ng m xt re s e tracted w th ethyl acetate The comb e organ layers are washed with brine and d d with Na_2SO Purification by flash column w th hexane/ethyl acetate give product as clear o l Rf 0 4(hexane/ethyl acetate 12 1)

Step I

A mixture of bromide (9 26g) tetrabutylammonium bromide (5 95g) K_2CO_3(6 12g) $Pd(OA)_2$(1 0g) i DMF(80ml) is heated at 80°C under N2 atmosphere fo 20 m utes The reactio mixture s cooled to room temperature and diluted w th water The resulting mixture is extracted with ethyl acetate The comb n organic layers are w hed w th brine a d d ed

with Na_2SO Purification by flash column with hexane/ethyl acetate gives product as clear oil LCMS m/z 548 4 (M+H)

Step J

To a solution of *t* BuLi(1 7M/pentane 7ml)in THF (30ml) at 78°C is added a solution of brom de (3 07g) in THF (5ml) The resulting mixture is stirred at 78°C for 10 minutes before iodoi ethane (1 4ml) is added Th reaction is continued for 30minutes The reaction is carefully quen hed with EtOH The resulting mixture is washed with water and brine dried with Na_2SO_4 Pur fi tion by flash column with hexane/ethyl acetate gives product as clear oil Rf 0 4(hexane/ethyl acetate 10 1)

Step K

Starting material (1 26g) is taken in THF (50ml) followed by the add tion of tetrabutyl mi on u fluor d (1 5 eq) t room te perature The react on is omplete fter 4 hours The reaction mixture is washed w th wate brine and dried with Na_2SO_4 P rification by flash column with hexane/ethyl acetate gives product. LCMS m/z 368 3 (M+H)

Step L

Starting aterial (100 ig) is take i in a hydrous DMF (4ml) NaH (52n g, 60%) is added followed by the additioi of CH_3I (5 equiv) The reaction is continued overnight. The reaction is quenched with water and extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column w th hexane/ethyl acetate gives product as lear o l LCMS m/z 382 3 (M+H)

EXAMPLE 50

The compounds show in the table are analogously prepared according to the procedures given in the above schemes and further illustrated in the above examples

with Na SO_4 Purification by flash column with hexane/ethyl acetate gives product as clear oil LCMS m/z 548 4 (M+H)

Step J

To solution of *t* BuLi(1 7M/pe tane 7ml)in THF (30ml) at 78°C is added solution of bromide (3 07g) n THF (5ml) The resulting mixture s st rred at 78°C for 10 minutes before iodomethane (1 4ml) is added The reaction is continued fo 30m nutes The reaction is carefully q nched with EtOH The res lt g mixture s washed with wate and brine, dried w th N_2SO Pu f cat by flash col mn w th hex ne/ethyl cetate g es prod ct as clea oil Rf 0 4(hexane/ethyl acetate 10 1)

Step K

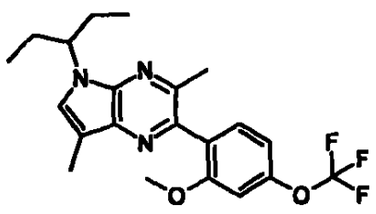
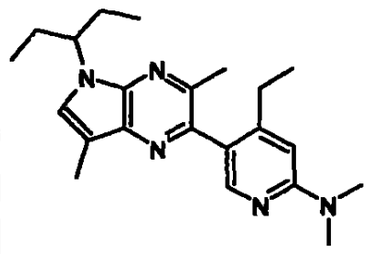
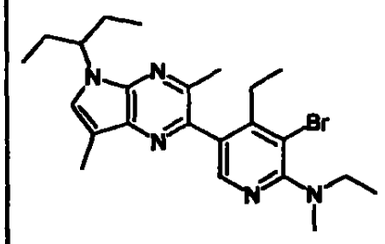
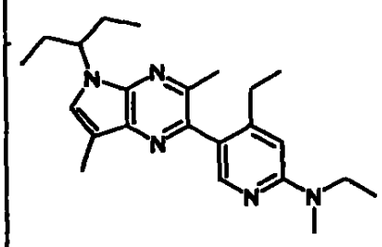
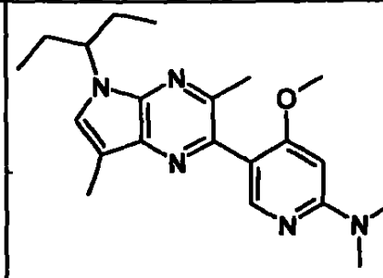
Start ng mater al (1 26g) i take i THF (50ml) followed by the dd t on of tetrabutylammon m fluoride (1 5 equi) at room temperature The reaction complete after 4 ho rs Th react on mixture wa hed with wate bri d d ied w th N SO Purification by flash column with hexane/ethyl acetate gives prod ct LCMS m/z 368.3 (M+H)

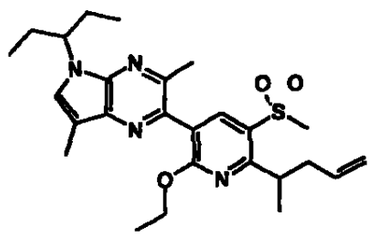
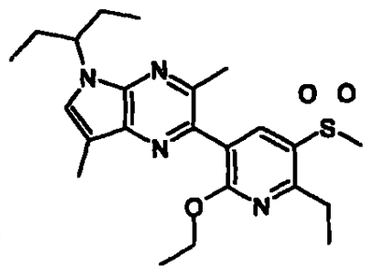
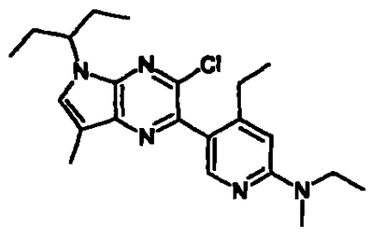
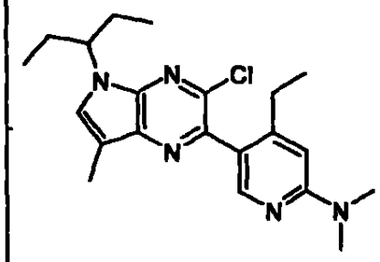
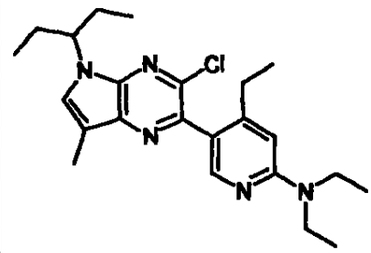
Step L

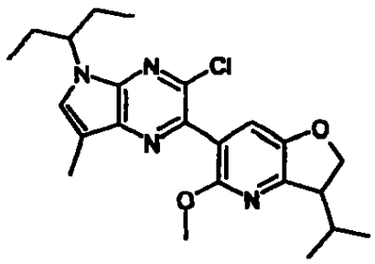
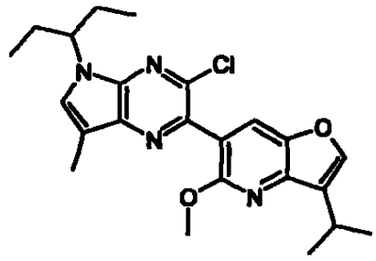
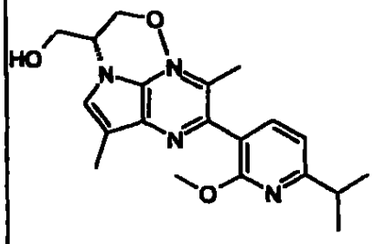
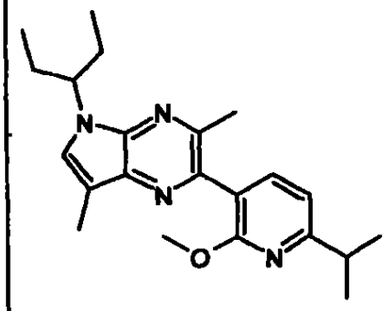
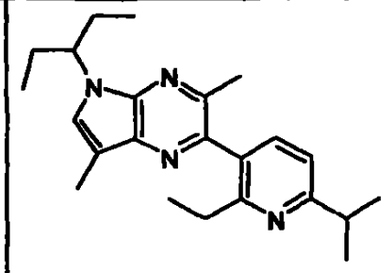
Starting material (100mg) is taken in anhydrous DMF (4ml) N H (52mg 60%) is added followed by the addition of CH_3I (5 equi) The reaction is continued overnight. The reaction is quenched with water and extracted with ethyl acetate The combine organic layers are washed with brine and dried with Na_2SO_4 Purification by flash column with hexane/ethyl acetate g ves product a lea oil LCMS m/z 382 3 (M+H)

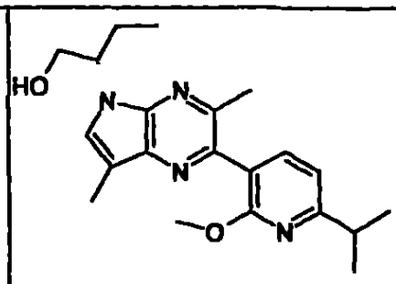
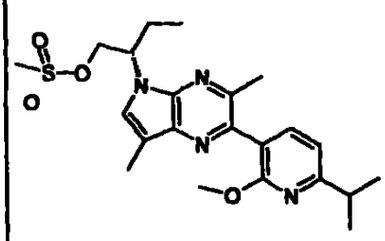
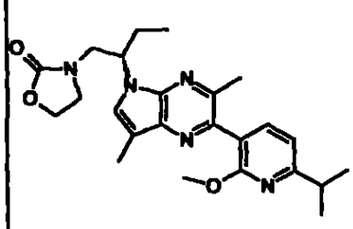
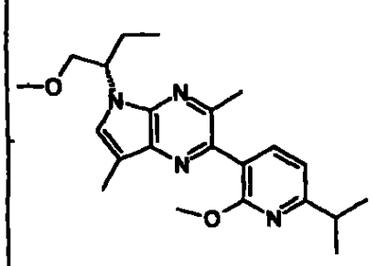
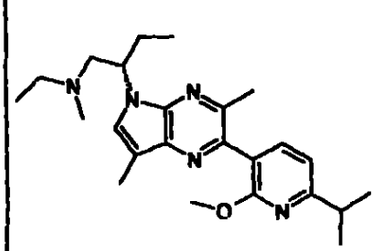
EXAMPLE 50

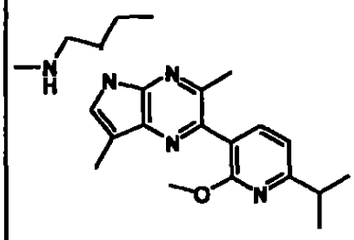
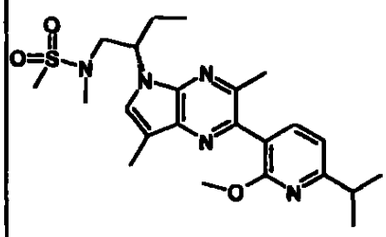
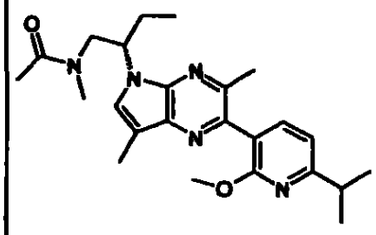
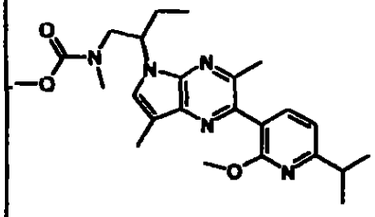
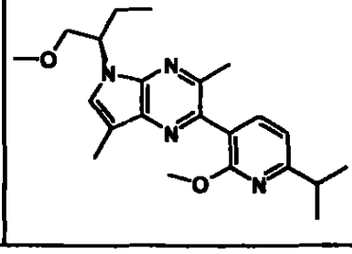
The compound shown n the table are analogously prepared according to the procedures given in the above schemes nd further illustrated in the above examples

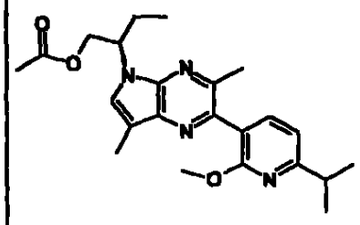
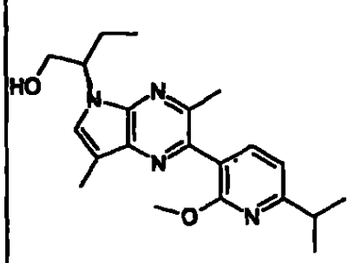
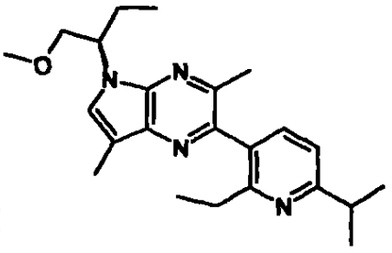
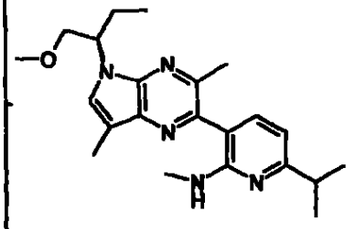
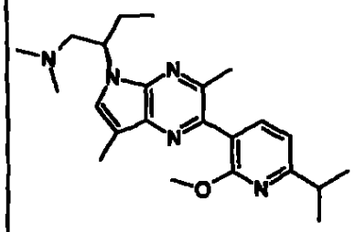
Cmpd #	STRUCTURE	COMPOUND NAME	MS m/z	Rt(min)
101		5-(1 Ethyl propyl)-2 (2-methoxy-4 trifluoromethoxy phenyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyrazine	408.21	1 77
102		{4-Ethyl 5 [5-(1-ethyl-propyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyrazin 2 yl] pyr di - 2 yl}-dimethyl-amine	366 22	1 41
103		{3 Bromo-4-ethyl 5 [5 (1-ethyl propyl)-3 7 dimethyl 5H pyrrol [2 3-b]pyraz 2 yl] pyridin 2 yl} ethyl me thyl-amine	458 12	1 94
104		Ethyl {4-ethyl 5 [5 (1 ethyl-propyl)-3 7 dimethyl 5H py rolo[2,3 b]pyrazin 2 yl]-pyridin 2 yl} methyl-amine	380 23	1 66
105		{5-[5-(1 Ethyl propyl)-3 7-dimethyl-5H pyrrolo[2,3 b]pyrazi 2 yl]-4 methoxy pyridin 2 yl}-d methyl amine	368 19	1 39

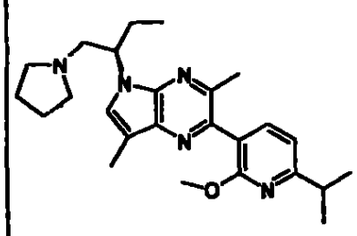
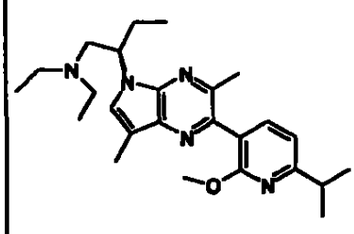
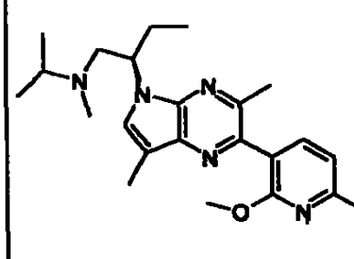
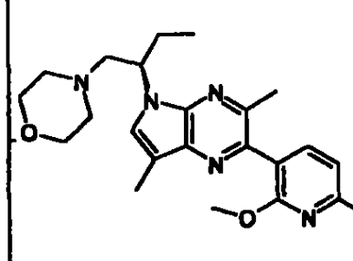
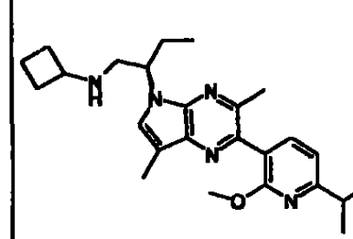
106		2 [2 Ethoxy 5 methanesulfonyl-6-(1 methyl but 3-enyl)-pyridin 3 yl]-5-(1 ethyl propyl)-3 7 dimethyl 5H pyrrolo[2 3 b]pyrazine	485 17	1 82
107		2-(2 Ethoxy-6-ethyl 5 methanesulfonyl pyridin 3 yl) 5-(1 ethyl-propyl)-3 7 dimethyl 5H pyrrolo[2 3 b]pyra i	445 16	1 74
108		{5 [3-Chloro-5-(1 ethyl propyl)-7 methyl 5H pyrrolo[2 3 b]pyrazin 2 yl]-4-ethyl pyrid 2 yl} ethyl m thyl mine	399 96	1 50
109		{5 [3-Chloro-5-(1 ethyl propyl)-7 methyl 5H pyrrolo[2 3 b]pyraz n 2 yl]-4-ethyl pyridin 2 yl} dimethyl-am ne	386 20	1 48
110		{5 [3-Chloro-5-(1 ethyl propyl)-7 methyl 5H pyrrolo[2 3 b]pyrazin 2 yl]-4-ethyl pyridin 2 yl -diethyl amine	414 23	1 51

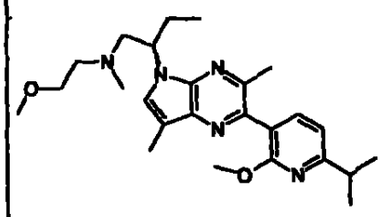
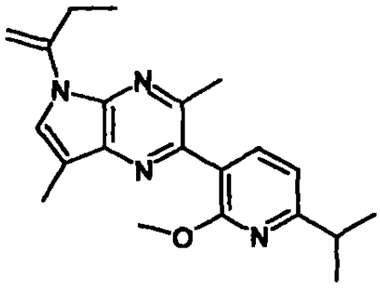
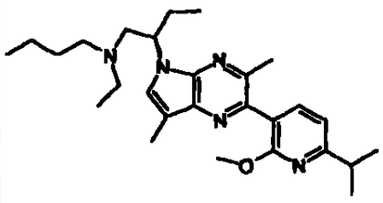
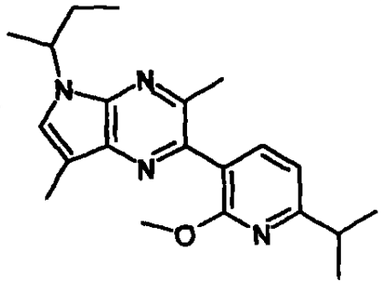
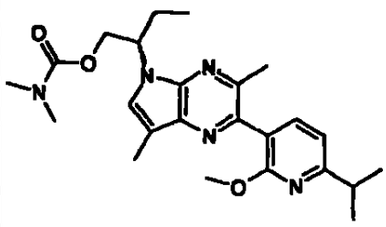
111		3 Chloro-5-(1-ethyl propyl)-2-(3 isopropyl 5 methoxy 2 3 dihydro-furo[3,2 b]pyridin-6-yl)-7 methyl 5H pyrrolo[2 3 b]pyrazine	429 08	1 53
112		3-Chloro-5 (1-ethyl propyl)-2-(3 isopropyl 5-methoxy furo[3 2 b]pyridin-6-yl)-7 methyl-5H-pyrrolo[2 3 b]pyrazine	427 12	1 52
113		(R)-2 [2-(6 Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl-pyrrolo[2,3 b]pyrazin 5 yl] 3 methoxy propan 1-ol	385 5	
114		5-(1 Ethyl-propyl)-2 (6- sopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl 5H pyrrolo[2 3 b]pyrazine	367 5	
115		2-(2 Ethyl-6-isopropyl pyridin 3 yl)-5 (1 ethyl propyl)-3 7 dimethyl 5H pyrrolo[2 3 b]pyrazine	365 5	

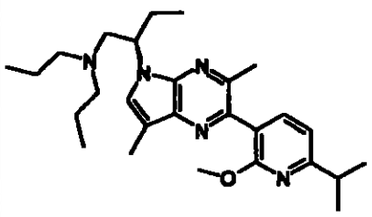
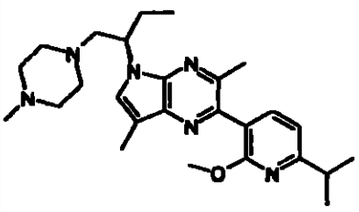
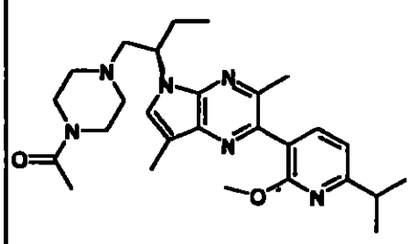
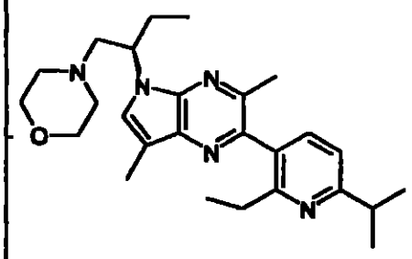
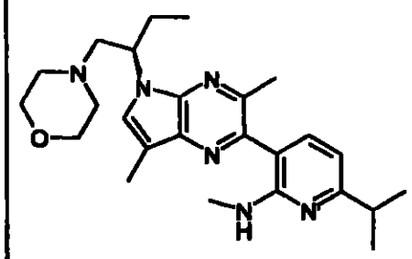
116		2 [(S)-2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-d methyl pyrrolo[2 3 b]pyrazin 5 yl] butan 1-ol	369 4	
117		Methanesulfo c acid 2 [(S) 2-(6- sopropyl 2-methoxy pyr din 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl]-butyl ester	447 4	
118		3 {2 [(S)-2 (6-Isopropyl 2 m thoxy pyridi 3 yl) 3 7 dim thyl pyrrolo[2,3 b]pyraz n 5 yl] butyl} oxazol d 2-one	438 4	
119		(S) 2 (6-Isopropyl 2 methoxy pyridin 3 yl)-5-(1 methoxymethyl propyl)-3 7-dimethyl 5H pyrrolo[2 3 b]pyra ine	383 2	
120		Ethyl {2 [(S) 2 (6-isopropyl 2 methoxy pyridin 3 yl)-3 7 dimethyl pyrrolo[2 3 b]pyrazin 5 yl] butyl} methyl-am ne	410 4	

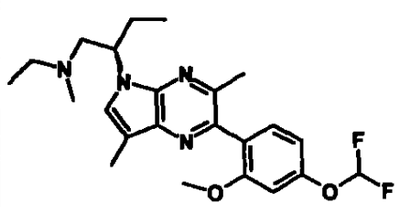
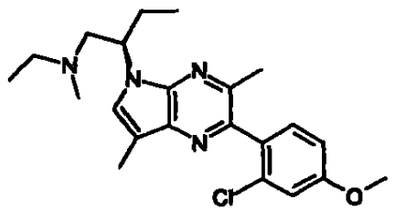
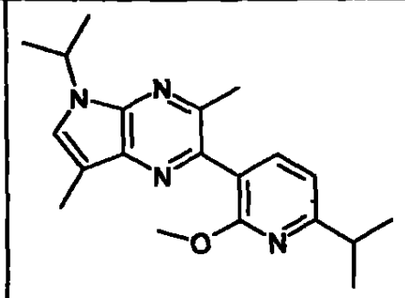
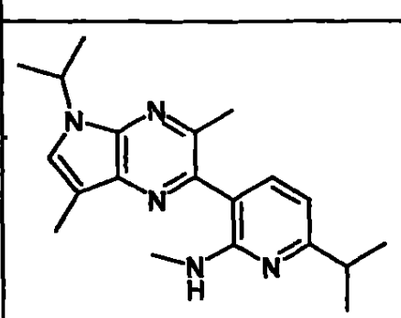
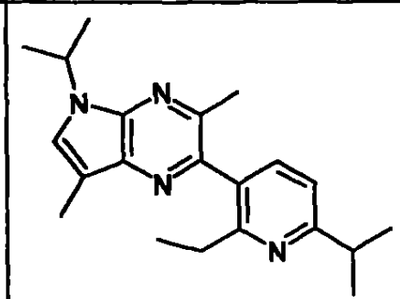
121		{2 [(S)-2 (6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin-5 yl] butyl}-methyl-amine	382 3	
122		N {2 [(S) 2-(6-Isopropyl-2 methoxy-pyridin 3 yl)-3 7 dimethyl pyrrolo[2,3 b]pyrazin 5 yl] butyl} N methyl methanesulfonamide	460 3	
123		N {2 [(S) 2-(6-Isopropyl-2-methoxy pyridin 3 yl)-3 7 dimethyl pyrrolo[2 3 b]pyrazin 5 yl] b tyl} N methyl-acetamide	424 5	
124		{2 [(S)-2-(6-Isopropyl 2-methoxy pyr din 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin 5 yl] butyl}-methyl carbamic acid methyl ester	440 4	
125		(R) 2-(6-Isopropyl 2 methoxy pyridin 3 yl)-5-(1 methoxymethyl propyl)-3 7-dimethyl 5H pyrrolo[2 3 b]pyrazine	383 3	

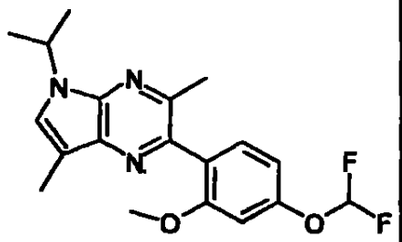
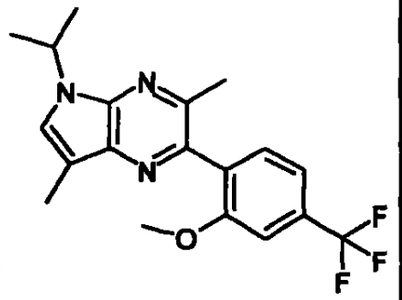
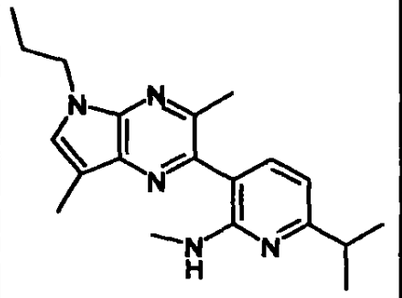
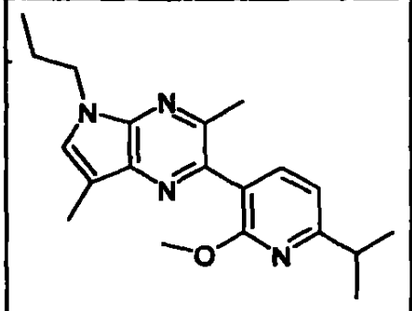
126		Acetic acid 2 [(R)-2-(6 isopropyl 2-methoxy pyrid n 3 yl)-3 7 dimethyl pyrrolo[2,3 b]pyrazin 5 yl]-butyl ester	411 4	
127		2 [(R) 2-(6-Isopropyl 2-methoxy pyrid n 3 yl) 3 7 dimethyl pyrrolo[2,3 b]pyraz 5 yl] butan 1-ol	369 4	
128		(R)-2-(2 Ethyl-6-isopropyl-pyrid 3 yl)-5-(1 methoxymethyl propyl) 3 7-d methyl 5H pyrrolo[2 3-b]pyrazine	381 4	
129		{6-Isopropyl 3 [(R)-5 (1 methoxymethyl propyl)-3 7-dimethyl 5H-pyrrolo[2 3 b]pyraz n-2 yl] pyrid 2 yl} methyl-amine	382 3	
130		{2 [(R)-2-(6 Isopropyl 2 methoxy pyrid n 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyraz n 5 yl] butyl}-dimethyl amine	396 4	

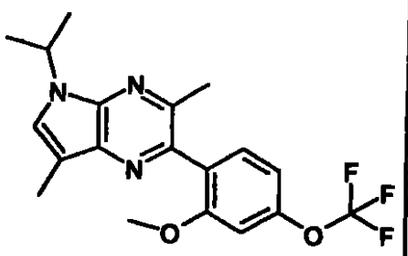
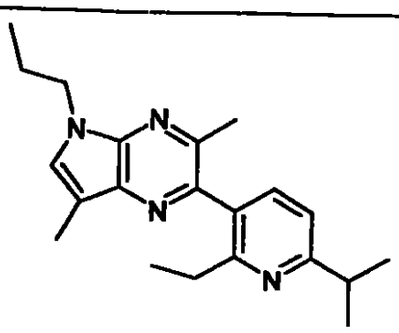
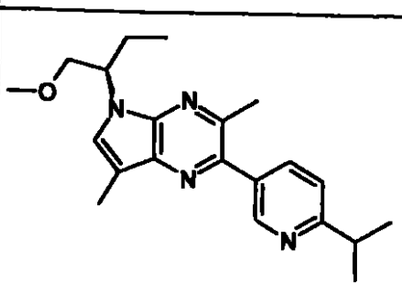
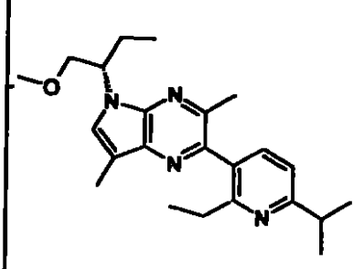
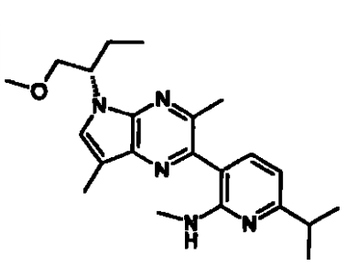
131		(R)-2-(6 Isopropyl 2 methoxy pyrid n 3 yl)-3 7-d methyl 5-(1 pyrrolidi 1 ylmethyl propyl)-5H pyrrolo[2,3-b]pyrazine	422.2	
132		Diethyl {? [(R) 2-(6 isopropyl 2 methoxy pyrid n 3 yl) 3 7 dimethyl pyrrolo[2 3 b]pyrazin-5-yl] butyl} amine	424 1	
133		Isopropyl {2 [(R)-2-(6 isopropyl 2 m thoxy pyrid 3 yl)-3 7 dimethyl pyrrolo[2,3 b]pyrazin 5 yl] butyl} methyl-amine	424 3	
134		(R)-2 (6-Isopropyl 2 methoxy pyr di 3 yl)-3 7-dimethyl 5-(1 morpholin-4-ylmethyl propyl)-5H pyrrolo[2 3 b]pyrazine	438 5	
135		Cyclobutyl {2 [(R) 2 (6-isopropyl 2 methoxy pyr din 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin 5 yl] butyl}-amine	422 5	

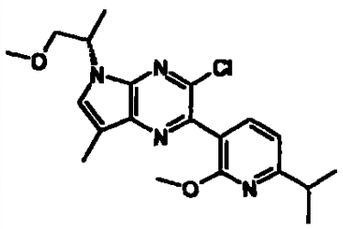
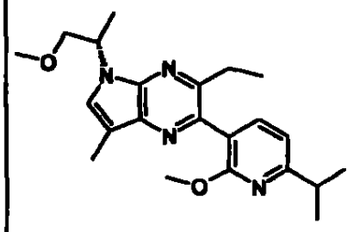
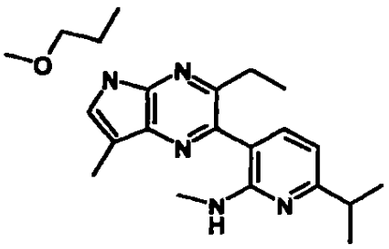
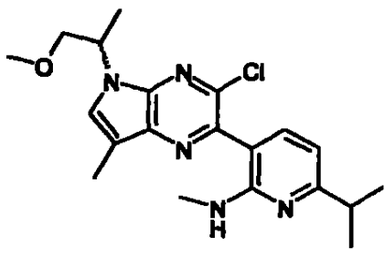
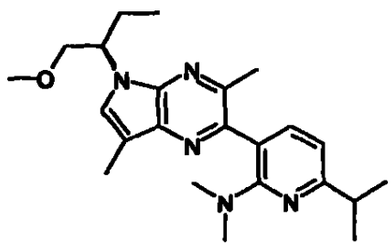
136		{2 [(R)-2-(6 Isopropyl 2 methoxy-pyrid n 3 yl)-3 7 d methyl pyrrolo[2 3 b]pyrazi 5 yl] butyl}-(2 methoxy-ethyl) methyl amine	440 4	
137		2 (6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-d methyl 5-(1 methylene-propyl)-5H pyrrolo[2 3 b]pyrazine	351 4	
138		B tyl-ethyl {2 [(R) 2 (6-isopropyl 2 methoxy pyridin 3 yl)-3 7-d methy l pyrrolo[2,3 b]pyraz n-5 yl] butyl}-amine	452 5	
139		5-sec-Butyl 2-(6 isopropyl 2-methoxy pyridin 3 yl) 3 7 d methyl 5H pyrrolo[" 3-b]pyraz ne	353 4	
140		D methyl-carbam c acid 2 [(R) 2-(6-isopropyl 2-methoxy pyrid n 3 yl)-3 7 d methyl pyrrolo[2 3 b]pyrazin 5 yl] butyl ester	440 4	

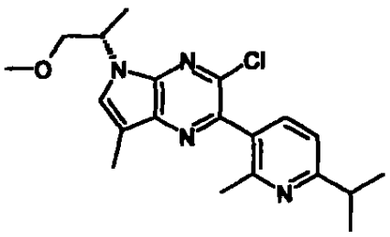
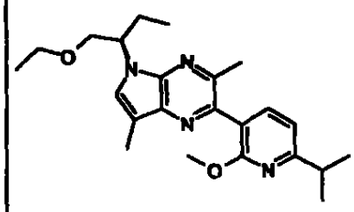
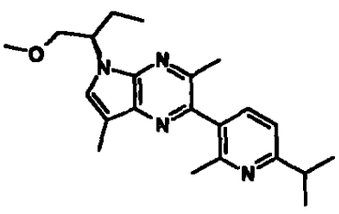
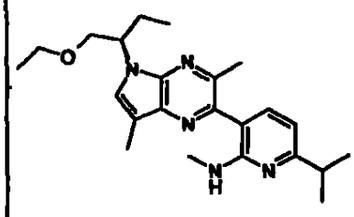
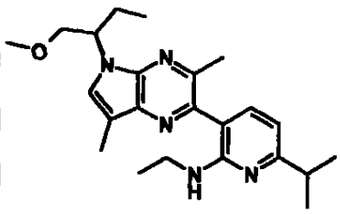
141		{2 [(R) 2-(6-Isopropyl-2-methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin-5 yl] butyl}-dipropyl amine	452 5	
142		2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl 5 [(R) 1 (4-methyl p perazin 1 ylmethyl)-propyl] 5H pyrrolo[2 3 b]pyrazine	451 5	
143		1-(4 {(R)-2 [2-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7 dimethyl pyrrolo[2 3 b]pyrazi 5 yl] b tyl} p peraz n 1 yl)-ethanone	479 5	
144		2-(2 Ethyl-6- sopropyl pyrid 3 yl)-3 7 di nethyl 5-((R)-1 morpholin-4 ylmethyl propyl)-5H pyrrolo[2 3 b]pyrazine	436 4	
145		{3 [3 7 Dimethyl 5 ((R) 1 morpholin-4 ylmethyl propyl) 5H pyrrolo[2 3 b]pyrazin-2 yl]-6-isopropyl pyridin 2 yl} methyl-amine	437 3	

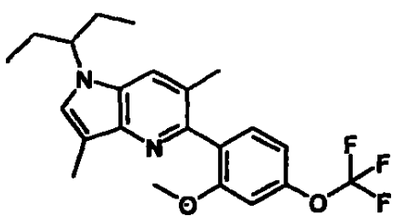
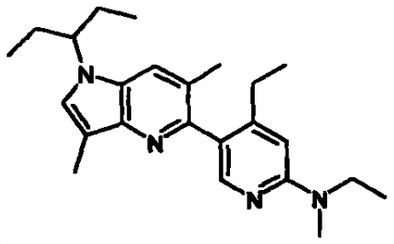
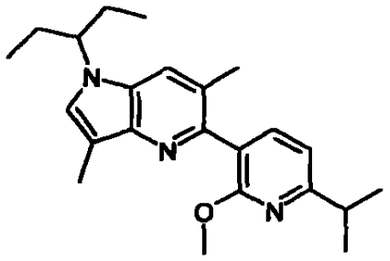
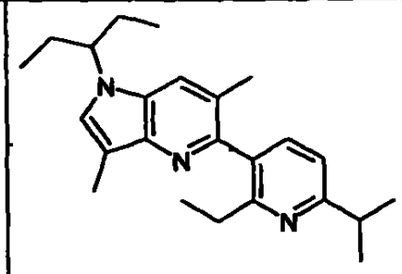
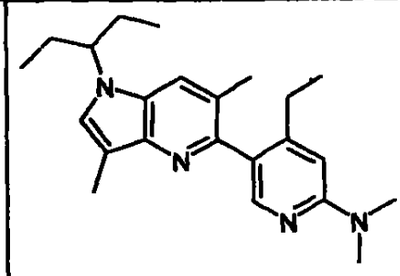
146		{(R) 2 [2-(4 Difluoromethoxy 2 meth oxy phe yl)-3 7 dimethyl pyrrolo[2 3 b]pyraz n 5 yl] butyl} ethyl methyl-am e	4 3 5	
147		{(R)-2 [2 (2-Chloro-4 methoxy phenyl)-3 7 d methyl-pyrrolo[2,3 b]pyrazı 5 yl] butyl} ethyl methyl-amine	401 5 403 5	
148		5 Isopropyl 2 (6 isopropyl 2 methoxy pyrid 3 yl) 3 7 d methyl 5H pyrrolo[2 3 b]pyraz ne	339 1	
149		[6 Isopropyl 3-(5 isopropyl 3 7-dimethyl 5H pyrrolo[2,3 b]pyrazı 2-yl)-pyridı 2 yl] methyl-amine	338 3	
150		2-(2 Ethyl-6 isopropyl pyridin 3 yl)-5 isopropyl 3 7-dimethyl 5H pyrrolo[2,3 b]pyraz e	337 2	

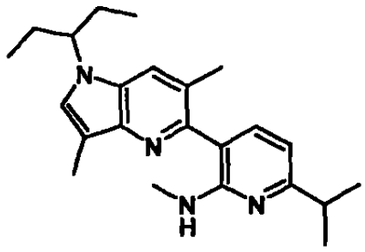
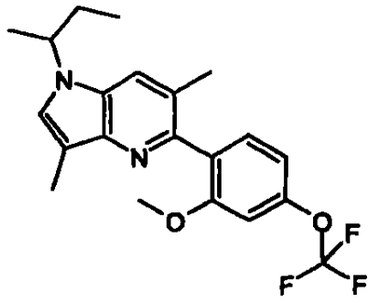
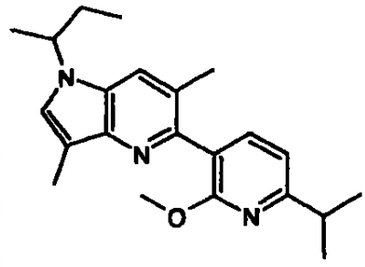
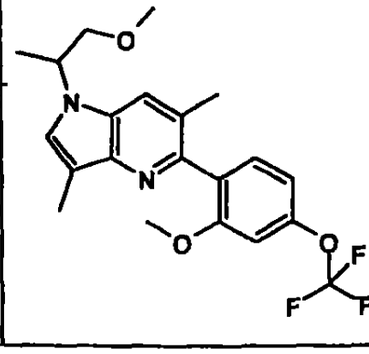
151		2-(4 Difluoro nethoxy 2-methoxy phenyl)-5 isopropyl 3 7-dim thyl 5H pyrrolo[2 3 b]pyrazine	362 1	
152		5 Isopropyl 2-(2 m thoxy-4 trifluoromethyl phenyl)-3 7-dim thyl 5H pyrrolo[2,3 b]pyrazine	364 1	
153		[3-(3 7 Dimethyl 5 propyl 5H-pyrrolo[2 3 b]pyrazin 2 yl)-6-isopropyl pyridi 2 yl] methyl-am ne	338 1	
154		2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-dim thyl 5 propyl 5H pyrrolo[2,3 b]pyrazine	339 1	

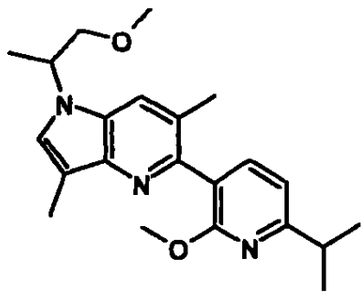
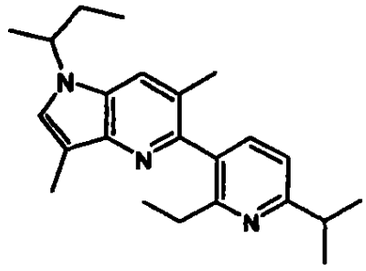
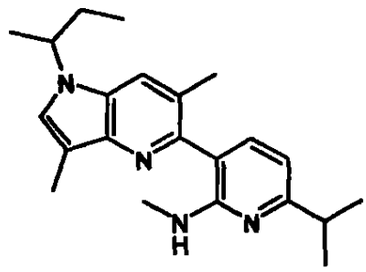
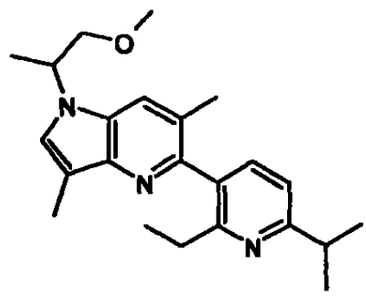
155		5 Isopropyl 2 (2 methoxy-4 trifluoromethoxy phenyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyraz ne	380 0	
156		2 (2 Ethyl-6-isopropyl pyridin 3 yl)-3 7 dimethyl 5 propyl 5H pyrrolo[2 3 b]pyrazine	337 2	
157		(R)-2-(6 Isopropyl py id 3 yl)-5 (1 methoxymethyl propyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyraz ne	353 3	
158		(S) 2-(2 Ethyl-6 isopropyl pyridin 3 yl)-5-(1-methoxymethyl propyl)-3 7-d methyl 5H pyrrolo[2,3 b]pyrazine	381 1	
159		{6-Isopropyl 3 [(S) 5 (1 methoxymethyl propyl)-3 7-dimethyl 5H pyrrolo [2 3 b]pyraz n 2 yl] pyridin 2 yl} methyl amine	382 3	

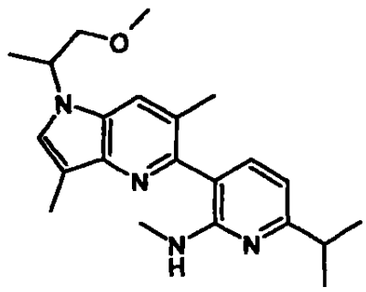
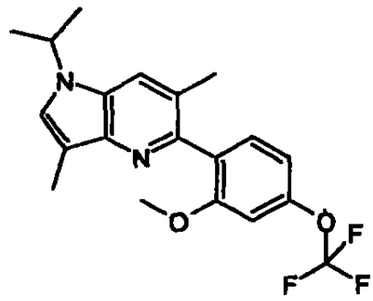
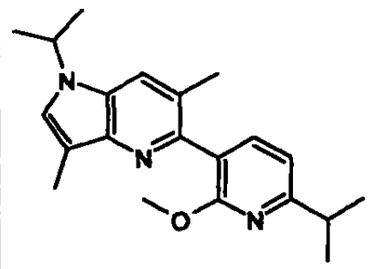
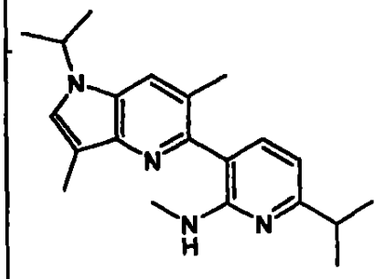
160		(S) 3-Chloro 2-(6-isopropyl 2-methoxy pyridin 3 yl)-5-(2 methoxy 1-methyl ethyl)-7 methyl 5H pyrrolo[2,3 b]pyrazine	389 4 391 4	
161		(S)-3 Ethyl 2-(6 isopropyl 2 methoxy pyridin 3 yl)-5-(2 methoxy 1 methyl ethyl)-7 methyl 5H pyrrolo[2 3-b]pyrazine	383 4	
162		{3-[3 Ethyl 5-((S)-2 methoxy-1-methyl ethyl)-7 methyl 5H pyrrolo[2 3 b]pyrazin 2 yl]-6-isopropyl pyr din 2 yl}-methyl-amin	382 4	
163		{3 [3-Chloro-5-((S)-2 methoxy 1 methyl ethyl)-7 methyl 5H pyrrolo[2 3 b]pyrazin 2 yl]-6-isopropyl pyridin 2 yl} methyl-amine	388 4 390 4	
164		{6-Isopropyl 3 [5 ((R) 1 m thoxymethyl propyl)-3 7-d methyl 5H pyrrolo [2 3 b]pyrazin 2 yl] pyridin 2 yl}-dimethyl amine	396 5	

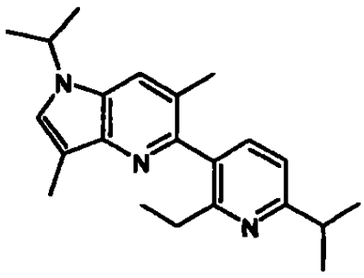
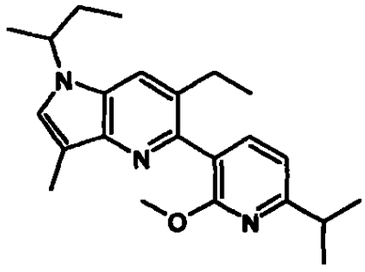
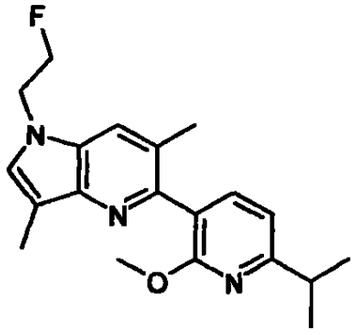
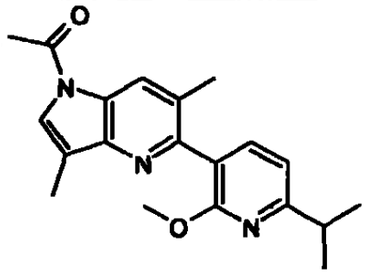
165		3-Chloro 2 (6-isopropyl 2 methyl pyrid n 3 yl)-5-((S)-2 methoxy 1 meth yl-ethyl) 7-methyl 5H pyrrolo[2 3 b]pyrazine	373 3 375.3	
166		5-((R)-1 Ethoxymethyl-propyl) 2-(6 isopropyl 2 methoxy pyrid n 3 yl)-3 ,7-dimethyl 5H pyrrolo[2 3 b]pyra ine	397.5	
167		2-(6 Isopropyl 2 methyl pyr d n 3 yl)-5 ((R)-1 methoxymethyl propyl)-3 ,7-d methyl 5H pyrrolo[2 3 b]pyraz e	367 5	
168		{3 [5-((R)-1 Ethoxymethyl propyl)-3 ,7-dimethyl 5H pyrrolo[2 3 b]pyraz n 2 yl]-6-isopropyl pyridin 2 yl}-methyl amine	396 5	
169		Ethyl {6-isopropyl 3 [5-((R) 1 methoxymethyl propyl)-3 7-d methyl 5H p yrrolo[2 3 b]pyrazin-2 yl] pyridin 2 yl} amin	396 5	

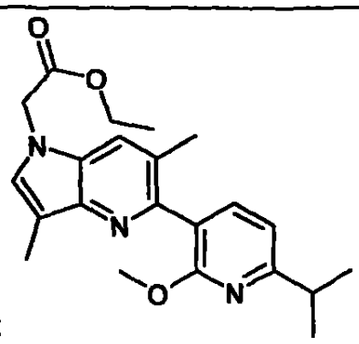
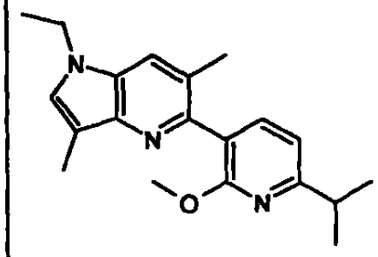
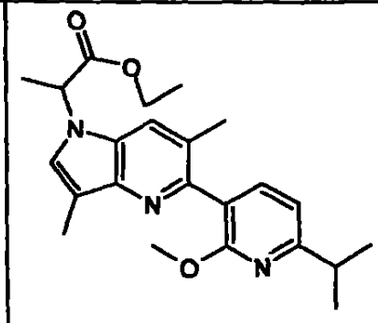
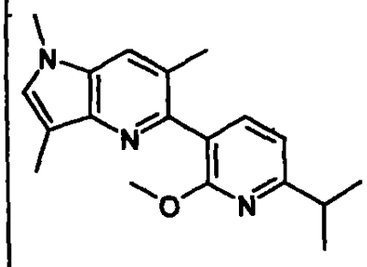
170		1-(1 Ethyl-propyl)-5 (2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine		
171		Ethyl {4-ethyl 5 [1 (1 ethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5-yl]-pyridin 2 yl} methyl-amine	379 5	
172		1-(1 Ethyl propyl)-5 (6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridine	366 4	
173		5-(2 Ethyl-6-isopropyl pyridin-3 yl)-1-(1 ethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	364 5	
174		{4-Ethyl 5 [1-(1-ethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl] pyridin 2 yl}-dimethyl amine	365 5	

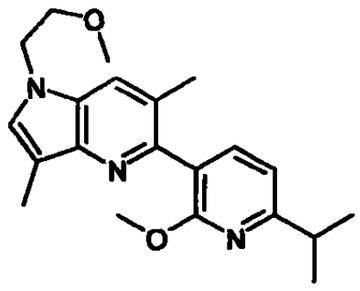
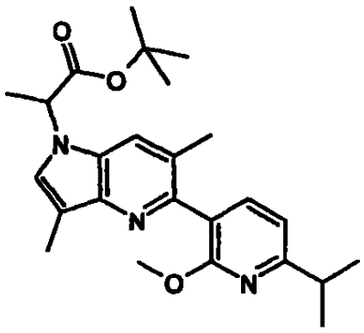
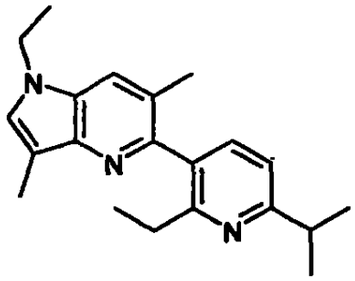
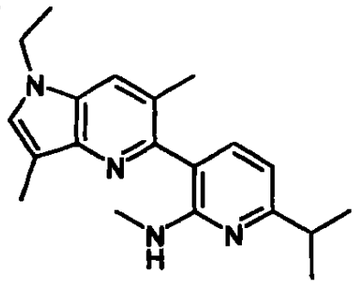
175		{3 [1-(1 Ethyl propyl) 3 6-d methyl 1H pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl pyr dm 2 yl} methyl amine	365 5	
176		1 sec-B tyl 5-(2 methoxy-4 trifluoromethoxy phenyl) 3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	393 3	
177		1-sec Butyl 5 (6 isopropyl 2 m th xy pyrid n 3 yl)-3 6 d m thyl 1H pyrrolo[3 2 b]py d	352 4	
178		1-(2 Methoxy 1 methyl-ethyl)-5-(2 methoxy-4 trifluoromethoxy phenyl)-3 ,6-d methyl 1H pyrrolo[3 2 b]py d e	409 3	

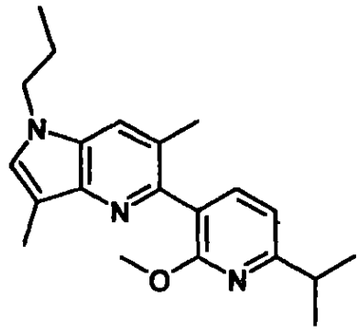
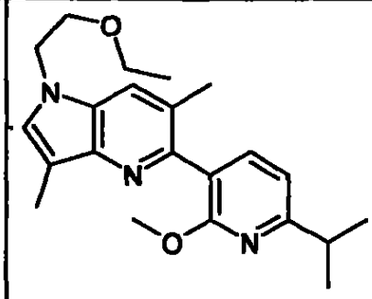
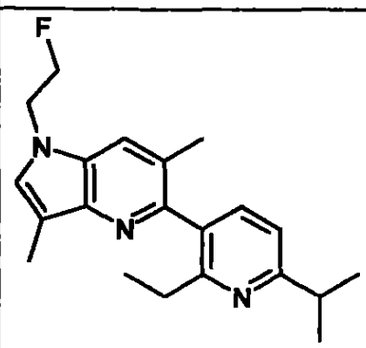
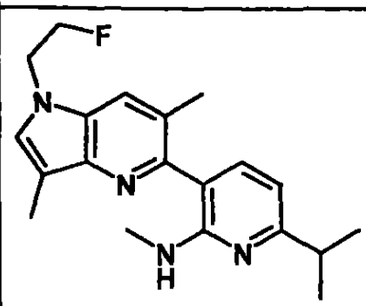
179		5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-(2-methoxy 1 methyl-ethyl)-3 6 dimethyl 1H pyrrolo[3 2-b]pyridine	368 1	
180		1-sec-Butyl 5-(2-ethyl-6-isopropyl pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridin	350 5	
181		[3-(1-sec B tyl 3 6-d methyl 1H pyrrolo[3 2 b]pyr d n 5 yl)-6-isopropyl pyridin-2 yl] methyl amine	351 4	
182		5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1-(2 methoxy 1 methyl ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	366 3	

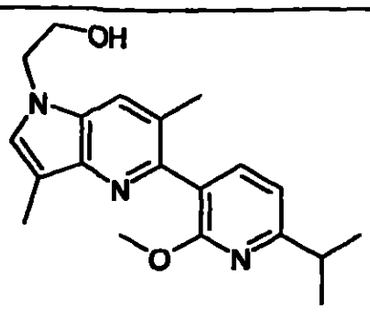
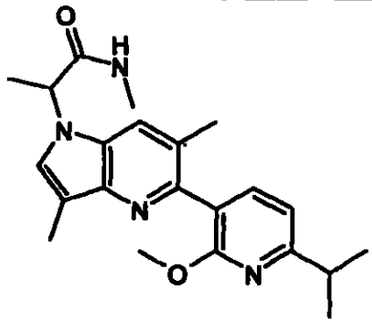
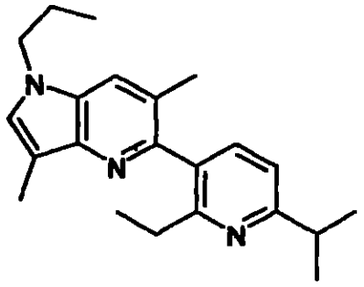
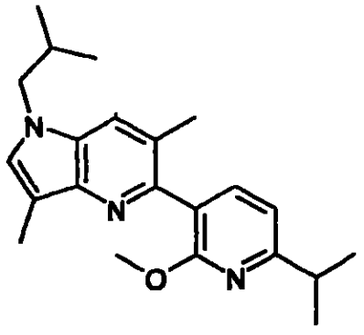
183		{6-Isopropyl 3 [1-(2 methoxy-1 methyl ethyl)-3 6-d methyl 1H pyrrolo[3 ,2 b]pyrid n 5 yl] pyridin 2 yl} methyl amine	367 5	
184		1 Isopropyl 5 (2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl 1H pyrrol [3 2 b]pyridine	379 4	
185		1 Isopropyl 5 (6 isopropyl 2 methoxy pyrid 3 yl) 3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	338 3	
186		[6 Isopropyl 3-(1 isopropyl 3 6-dimethyl 1H pyrrolo[3 2 b]pyrid n 5 yl) pyridi 2 yl] methyl am	337 4	

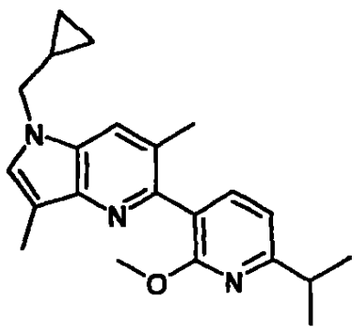
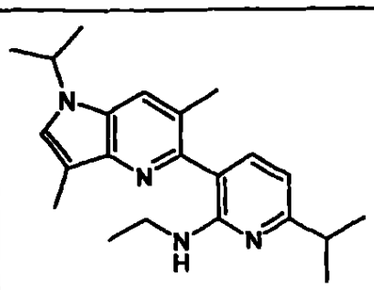
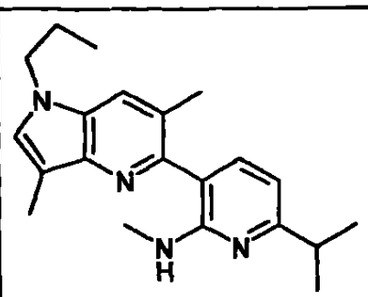
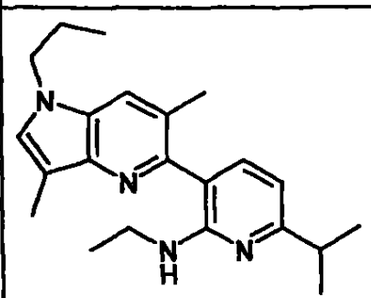
187		5-(2 Ethyl-6-isopropyl pyridin-3 yl)-1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	336 4	
188		1-sec Butyl-6-ethyl 5 (6-isopropyl 2 methoxy pyr din 3 yl)-3-methyl 1H pyrrolo[3,2-b]pyridine	366 4	
189		1-(2 Fluoro-ethyl) 5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	342 4	
190		1 [5-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyrid 1 yl]-ethanone	338 3	

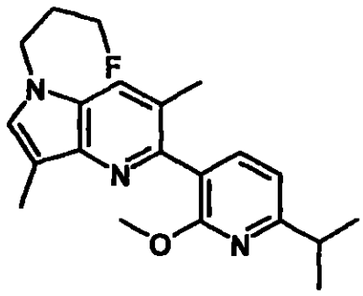
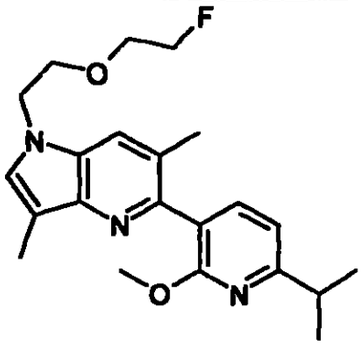
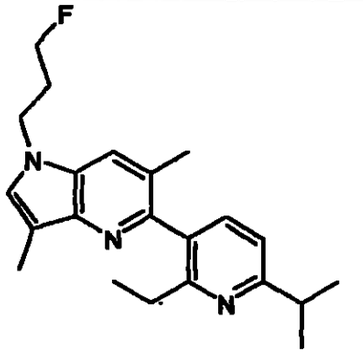
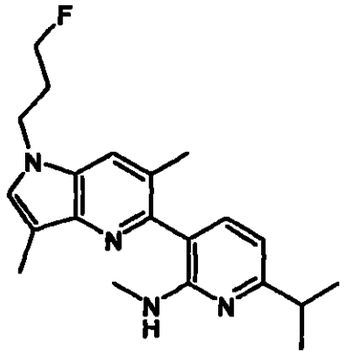
191		[5-(6-Isopropyl 2 methoxy-pyridin 3 yl) 3 6-dimethyl pyrrolo[3 2 b]pyrid n 1 yl]-acetic acid ethyl ester	382.3	
192		1 Ethyl 5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyr d	324 4	
193		2-[5-(6-Isopropyl 2 methoxy pyrid 3 yl)- 3 6-d methyl pyrrolo[3 2 b]pyridin 1 yl] propion a d ethyl e t	396 4	
194		5 (6-Isopropyl 2 methoxy pyridin 3 yl) 1 3 6 trimethyl 1H pyrrolo[3 2 b]pyrid ne	310 4	

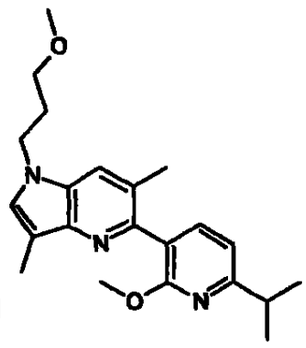
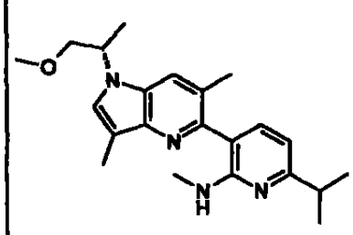
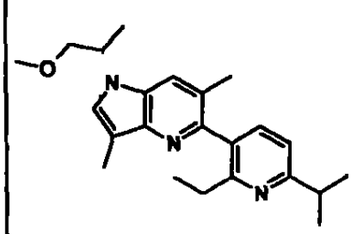
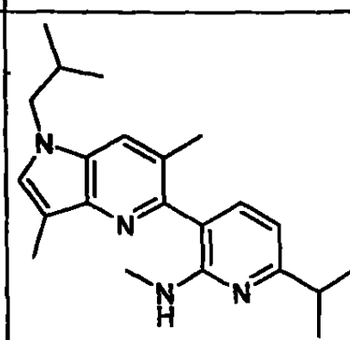
195		5 (6-Isopropyl 2 methoxy pyridin 3 yl)-1-(2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	354 1	
196		2 [5-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] propionic acid tert butyl ester	424.3	
197		1 Ethyl 5 (2-ethyl-6 isopropyl pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	322 5	
198		[3-(1 Ethyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl)-6-isopropyl pyridin 2 yl] methyl amine	323 5	

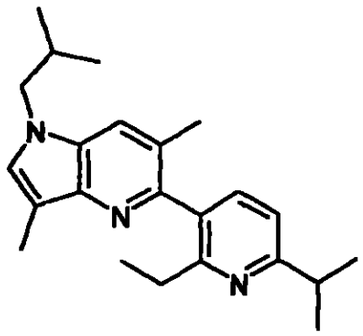
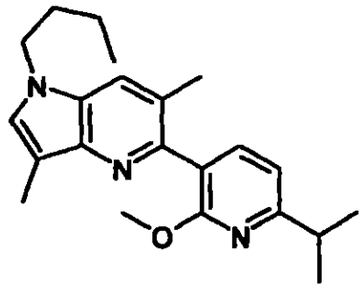
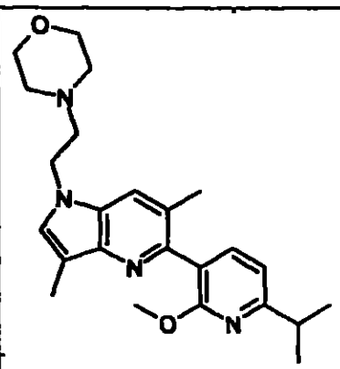
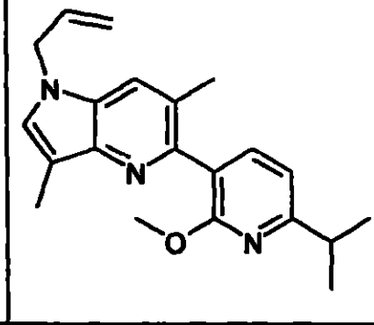
199		5-(6 Isopropyl 2 methoxy pyridı 3 yl)-3 6-d methyl 1 propyl 1H pyrrolo[3 2 b]py d ne	338 4	
200		1-(2 Ethoxy ethyl) 5 (6-ısopropyl 2 methoxy-pyrıdın 3 yl)-3 6-d methyl 1H pyrrolo[3 2 b]pyrıd ne	368 3	
201		5-(2 Ethyl-6 ısopropyl pyrıd n 3 yl)-1-(2 fluoro-ethyl)-3 6-dımethyl 1H pyrrol [3 2 b]pyrıd e	340 2	
202		{3 [1 (2 Fl oro-ethyl)-3 6-dımethyl 1H pyrrolo[3 2 b]pyrıd 5 yl]-6 sopropyl pyrıdı ? yl} methyl am ne	341 4	

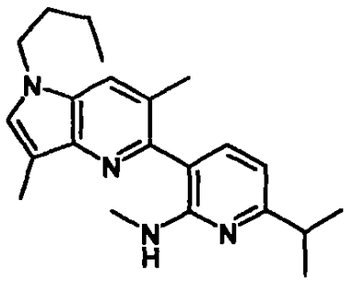
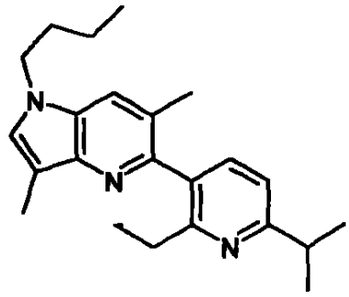
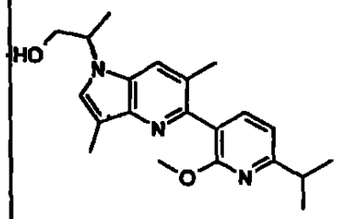
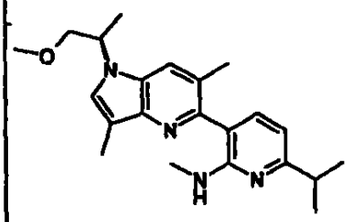
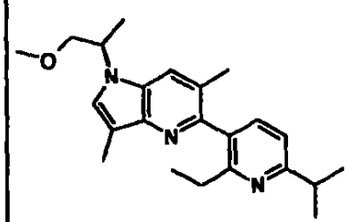
203		2 [5-(6-Isopropyl 2 methoxy-pyr din 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl]-ethanol	340 17	2 07
204		2 [5-(6 Isopropyl 2 m thoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl] N methyl propionamide	381 4	
205		5-(2 Ethyl-6-isopropyl pyridin 3 yl) 3 6-dimethyl 1 propyl 1H pyrrolo[3,2 b]pyridine	336 4	
206		1 Isobutyl 5 (6 isopropyl 2 methoxy pyr din 3 yl)-3 6 dimethyl 1H pyrrolo[3,2-b]py id	352 4	

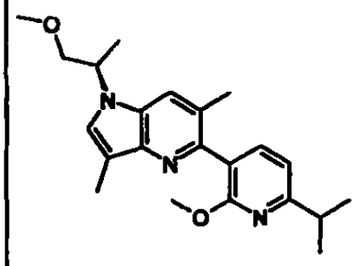
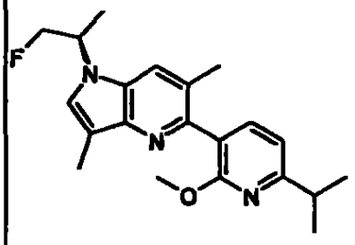
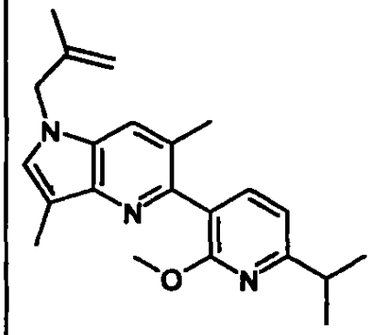
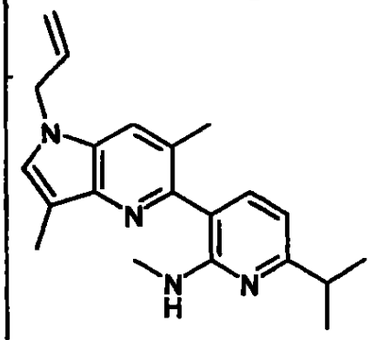
207		1-Cyclopropylmethyl 5-(6 isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyrid e	350 4	
208		Ethyl [6-isopropyl 3 (1 sopropyl 3 6-d methyl 1H pyrrolo[3 2 b]pyrid 5 yl) pyr d 2 yl] ami	351 4	
209		[3 (3 6 D methyl 1 propyl 1H pyrrolo[3 2 b]pyrid n 5 yl)-6 isopropyl pyridi 2 yl] methyl-amine	337 4	
210		[3-(3 6 D methyl 1 propyl 1H pyrrolo[3 2 b]pyridin 5 yl)-6 isopropyl pyrid n 2 yl] ethyl-amine	351 5	

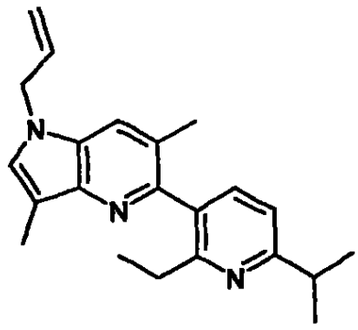
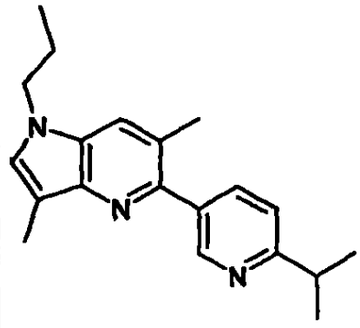
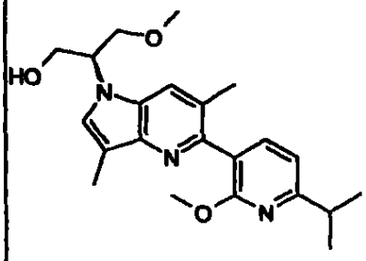
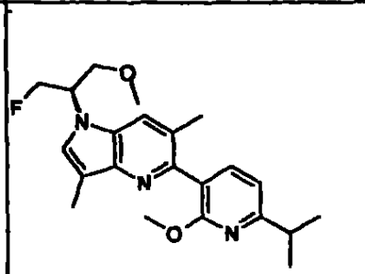
211		1-(3 Fluoro-propyl)-5 (6-isopropyl 2 methoxy pyr din 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	356 4	
212		1 [2-(2 Fluoro-ethoxy)-ethyl] 5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyrid ne	386 4	
213		5 (2 Ethyl-6- supropyl pyrid 3 yl) 1 (3 fluoro-propyl)-3 6 dimethyl 1H pyrrolo[3,2 b]pyrid ne	354 20	1 96
214		{3 [1 (3 Fluoro-propyl)-3 6-dim thyl 1H pyrrolo[3,2 b]py idin-5 yl]-6 isopropyl pyr din 2 yl} methyl-amine	355 19	1 79

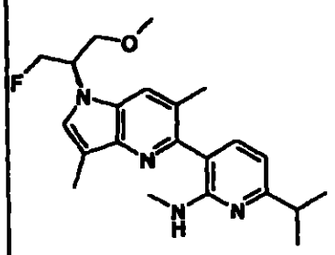
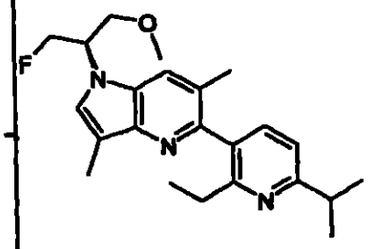
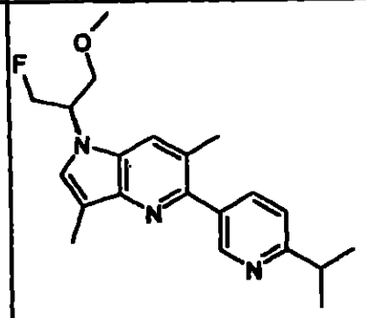
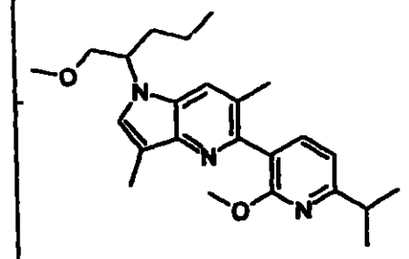
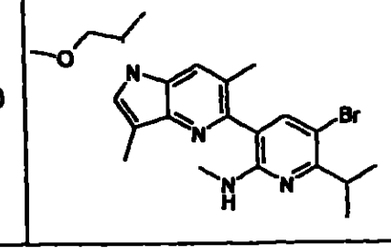
215		5-(6 Isopropyl 2 methoxy pyrid n 3 yl)-1-(3 methoxy propyl)-3 6-d m thyl 1H pyrrolo[3 2-b]pyridine	368 4	
16		{6-Isopropyl 3 [1-((S) 2 methoxy 1 methyl ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyrid n 5 yl] pyrid n 2 yl} methyl ami	367 2	
217		5-(2 Ethyl-6 sopropyl-pyridin 3 yl) 1 ((S) 2 methoxy 1 methyl ethyl)-3 6-d m thyl 1H pyrrolo[3 2 b]pyrid n	366 4	
218		[3-(1 Isobutyl 3 6 d methyl 1H pyrrolo[3 2 b]py idin 5 yl)-6- sopropyl -py id 2 yl] methyl-amine	351 5	

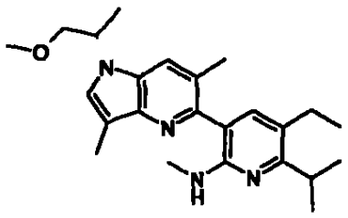
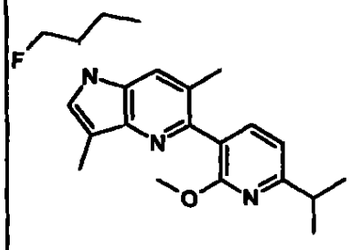
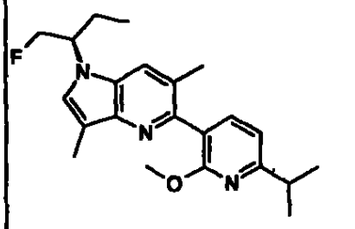
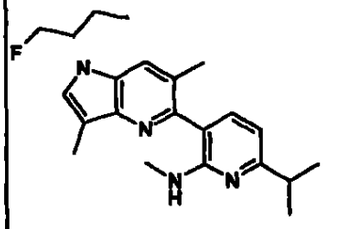
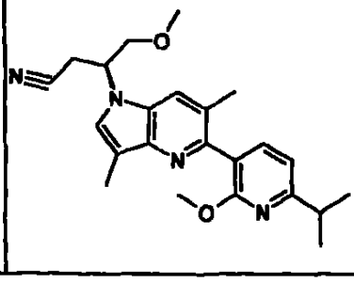
219		5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1 isobutyl 3 6-dimethyl 1H pyrrolo[3 2 b]pyr dine	350 5	
220		1 B tyl 5-(6- sopropyl-2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridin	352 4	
221		5-(6 Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1-(2 morpholin-4-yl-ethyl)-1H pyrrolo[3,2 b]pyr di ne	409 5	
222		1 Allyl 5-(6 isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyr din	Rf 0 33 (Hexane Ethyl ate 4 1)	

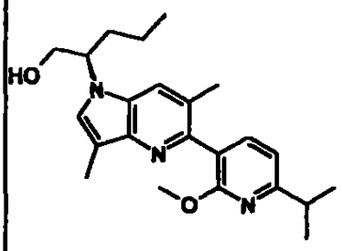
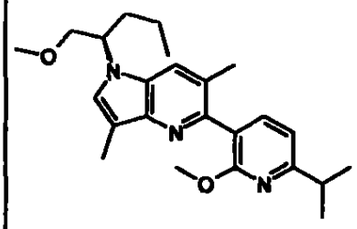
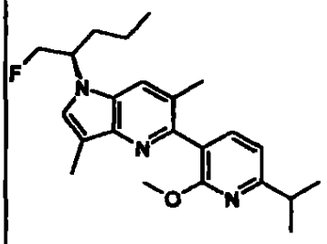
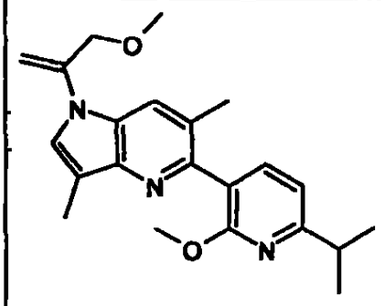
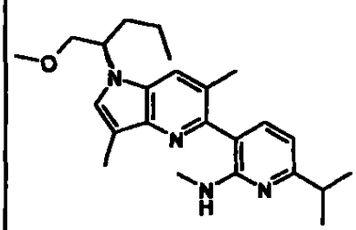
223		[3-(1 B tyl 3 6-d methyl 1H pyrrolo[3 2 b]pyrid n 5 yl)-6 isopropyl pyrid n 2 yl] methyl-amine	351 5	
224		1 Butyl-5-(2-ethyl-6 isopropyl pyridin 3 yl) 3 6-dimethyl 1H pyrrolo[3 2 b]py id ne	350 5	
225		(R)-2 [5-(6-Isopropyl 2 methoxy pyrid n 3 yl)-3 6-d methyl pyrrolo[3 2 b]pyr d 1 yl] propa 1-ol	354 4	
226		{6-Isopropyl 3 [1 ((R) 2 methoxy 1 methyl ethyl) 3 6-d methyl 1H pyrrolo[3 2 b]pyrid n 5 yl] pyridin 2 yl} methyl amine	367 5	
227		5-(2 Ethyl 6 sopropyl pyridin 3 yl) 1 ((R) 2 methoxy 1 methyl ethyl)- 3 6-d methyl 1H pyrrolo[3,2 b]pyrid ne	366 4	

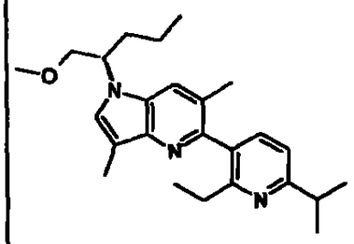
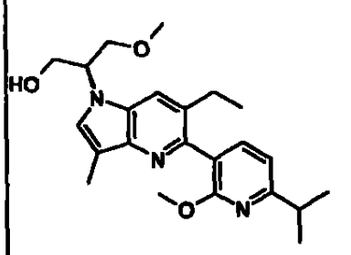
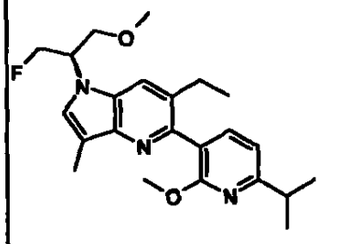
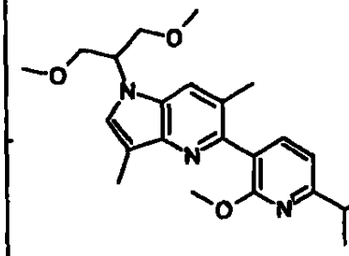
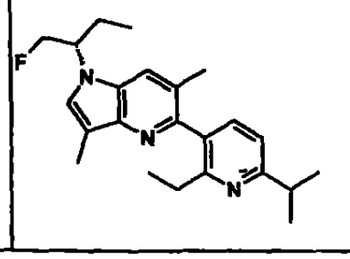
228		5-(6-Isopropyl 2 methoxy pyridin 3 yl)-1-((R)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	Rf 0 4 (Hexan Ethylacetate 2 1)	
229		1-((R) 2 Fl oro-1 methyl-ethyl) 5-(6-isopropyl 2 methoxy pyridin 3 yl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	356 4	
230		5-(6 Isopropyl 2 methoxy-pyr di 3 yl)-3 6-dimethyl 1-(2 methyl-allyl)-1H pyrrolo[3,2 b]py idu	350 5	
231		[3 (1 Allyl 3 6-dim thyl 1H pyrrolo[3,2-b]py idi 5 yl)-6-isopropyl pyridin-2 yl] methyl umine	335 3	

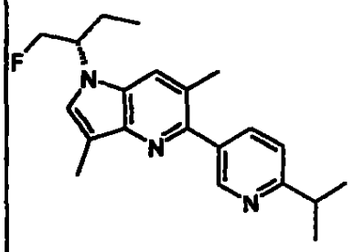
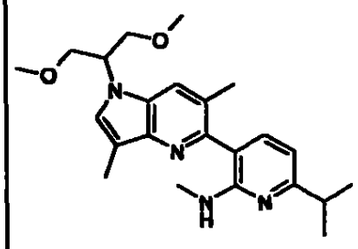
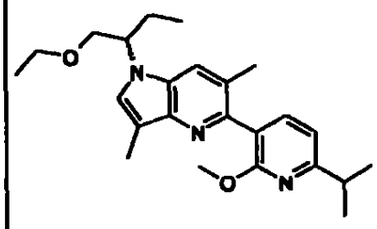
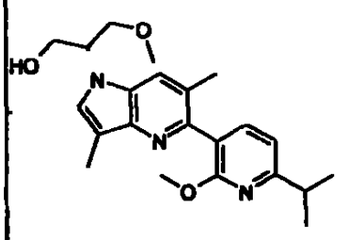
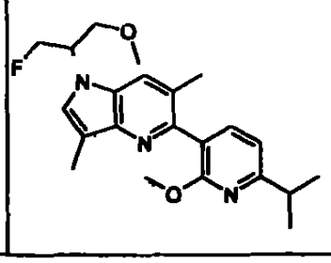
232		1 Allyl 5 (2-ethyl-6 isopropyl pyridin 3 yl) 3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	334 4	
233		5-(6-Isopropyl pyrid 3 yl)-3 6-dimethyl 1 propyl 1H pyrrolo[3 2 b]pyrid ne	308 3	
234		(S)-2 [5-(6-Isopropyl 2-methoxy pyrid n 3 yl)-3 6-d methyl pyrrolo[3 2 b]pyrid n 1 yl] 3 methoxy propan 1-ol	Rf 0 3 (Hexane/ ethyl cet te 1 1)	
235		1-((R)-1 Fluoromethyl 2 methoxy-ethyl)-5-(6-isopropyl 2 methoxy pyrid 3 yl) 3 6 d methyl 1H pyrrolo[3 2 b]py idine	386 6	

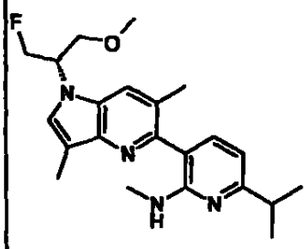
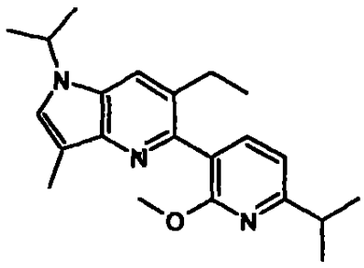
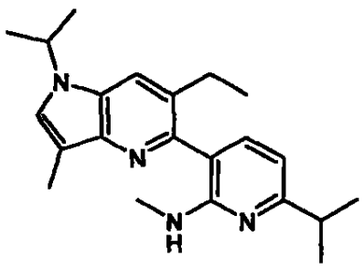
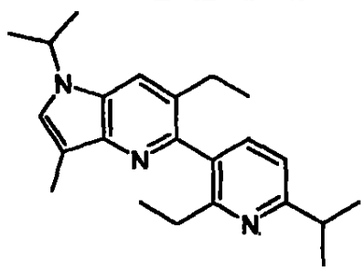
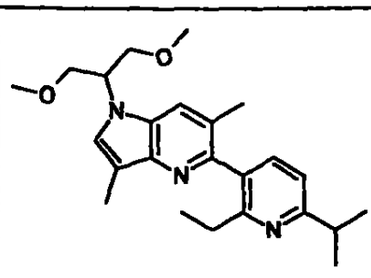
236		{3-[1-((R)-1 Fluoromethyl-2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl} methyl amine	385 5	
237		5 (2 Ethyl-6-isopropyl pyridin-3 yl)-1-((R)-1 fluoromethyl 2 methoxy-e thyl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	384 4	
238		1-((R)-1 Fluoromethyl 2 metho y-ethyl) 5 (6-isopropyl pyridin-3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyrid e	356 4	
239		5-(6-Isopropyl 2 methoxy pyr din 3 yl)-1-(1-methoxymethyl butyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	396 5	
240		{5 Bromo-6-isopropyl 3 [1-((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyrid n 5 yl] pyridin 2 yl} methyl-amine	445 3	

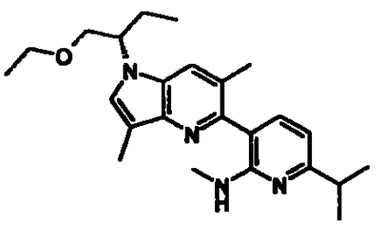
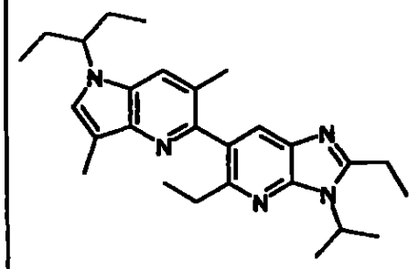
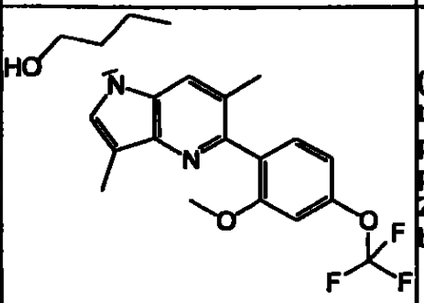
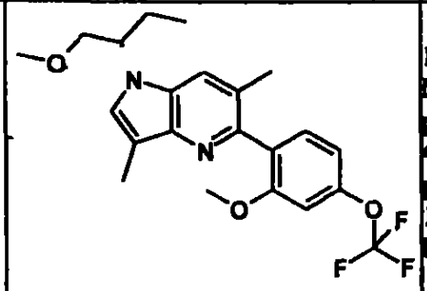
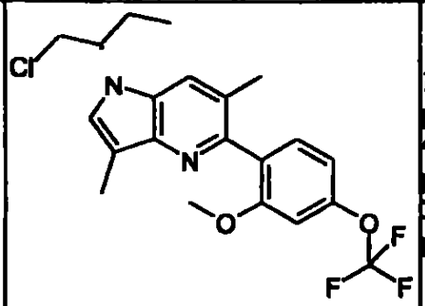
241		{5 Ethyl 6 isopropyl 3 [1-((S) 2 methoxy 1 methyl-ethyl)-3 6 d methyl 1H pyrrolo[3,2 b]pyrid n 5 yl] pyridin 2 yl} methyl-amine	395 5	
242		1-((S)-1 Fluoromethyl propyl)-5-(6 isopropyl 2 methoxy pyrid n 3 yl)-3 ,6-d methyl 1H pyrrolo[3,2 h]py d	370 44	1 55
243		1 ((R) 1 Fl oromethyl propyl) 5-(6 sopropyl 2 m thoxy py d n 3 yl)-3 6-dimethyl 1H pyrrol [3 2 h]py d ne	370 5	
244		{3 [1-((S) 1 Fluoromethyl propyl)-3 6-d methyl 1H pyrrolo[3 2 b]py d n 5 yl]-6-isopropyl pyrid n 2 yl} methyl am e	369 5	
245		(S) 3 [5 (6-Isopropyl 2 methoxy pyrid 3 yl)-3 6-dimethyl pyrrolo[3 2 h]pyridin 1 yl]-4 methoxy butyronitrile	393 4	

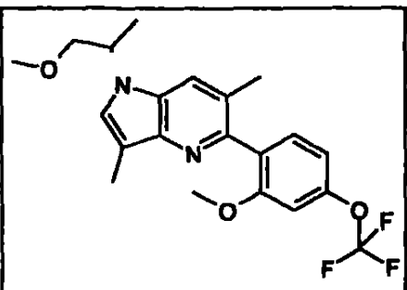
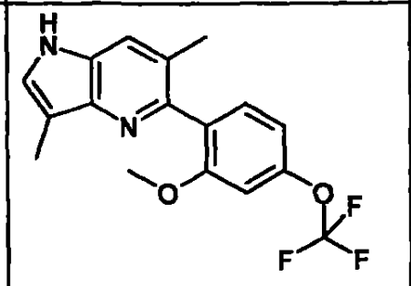
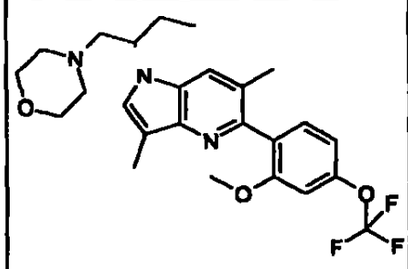
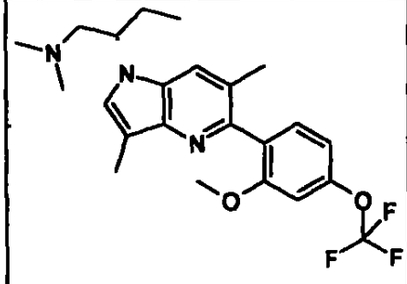
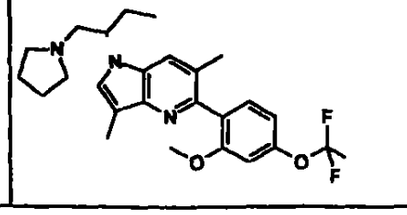
246		(R)-2 [5 (6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl]-pentan 1-ol	382 5	
247		5 (6 Isopropyl 2 methoxy pyridin 3 yl)-1-((R)-1 methoxymethyl butyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	396 5	
248		1-((R)-1 Fl oro t l yl butyl)-5 (6 isopropyl 2-methoxy-pyridin 3 yl)-3 6-d methyl 1H pyrrolo[3 2 b]pyridin	384 5	
249		5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-(1 methoxymethyl vinyl)-3 6-d methyl 1H pyrrolo[3,2 b]pyridine	366 4	
250		{6-Isopropyl 3 [1-((R)-1 methoxymethyl butyl)-3 6-dimeti yl 1H pyrrolo[3 2 b]pyridin 5 yl] pyridin 2 yl} m thyl-am	395 6	

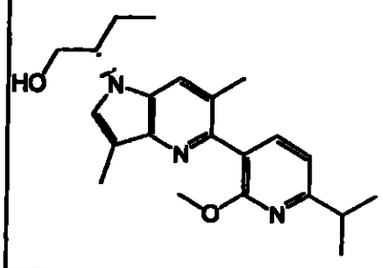
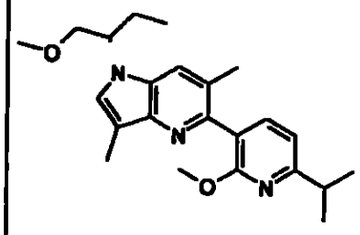
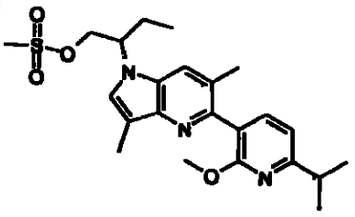
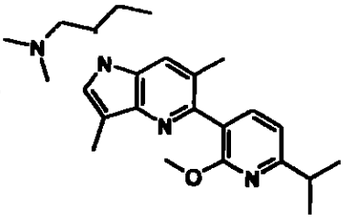
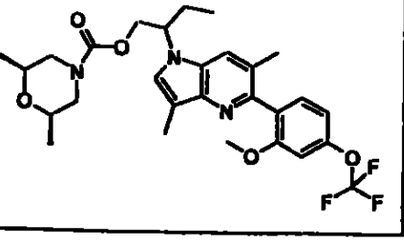
251		5-(2 Ethyl 6 isopropyl pyrid 3 yl) 1-((R) 1 meth xymethyl-butyl)-3 6 -dimethyl 1H pyrrol [3 2 b]pyridin	394 4	
252		(S) 2 [6 Ethyl 5-(6-isopropyl methoxy pyridi 3 yl) 3 methyl pyrrolo[3,2 b]pyrid n 1 yl] 3 methoxy propan 1-ol	Rf 0 4(Hex ane/Ethy l acetate 1 1)	
253		6-Ethyl 1-((R) 1 fluoromethyl 2 methoxy-ethyl) 5-(6 isopropyl 2 methoxy pyrid n 3 yl)-3-methyl-1H pyrrolo[3 2 b]py d ne	400 5	
254		5-(6-Isopropyl 2 methoxy pyrid 3 yl) 1-(2 methoxy 1 methoxymethyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b] pyr dine	398 5	
255		5-(2 Ethyl 6- sopropyl pyr d n 3 yl)-1 ((S)-1 fl oromethyl propyl)-3 6-dimethyl 1H pyrrol [3 2 b]pyridine	368 4	

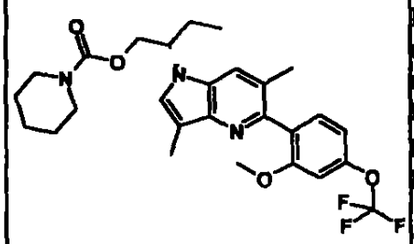
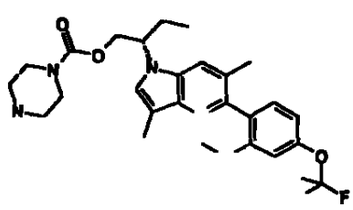
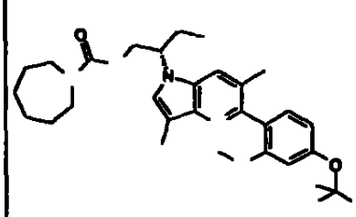
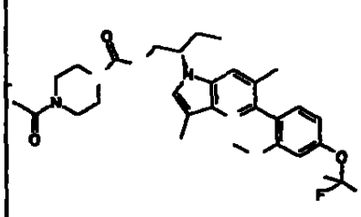
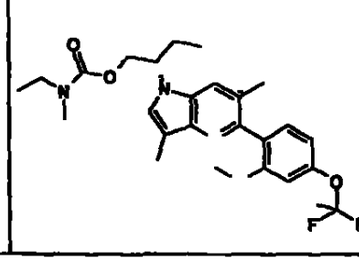
256		1-((S)-1 Fluoromethyl-propyl)-5-(6 isopropyl pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyrid n	340 4	
257		{6 Isopropyl 3 [1 (2 methoxy 1 methoxymethyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyrid n 5 yl] pyr du 2 yl} methyl-am ne	397 5	
258		1-((S)-1 Ethoxymethyl propyl)-5-(6 sopropyl 2 methoxy pyridin 3 yl)-3 6-di i ethyl 1H pyrrolo[3,2 b]pyridin	396 5	
259		(R)-2 [5-(6-Isopropyl 2 methoxy py din 3 yl) 3 6-dimethyl pyrrolo[3,2 b]py d 1 yl] 3 meti oxy propan 1-ol	384 4	
260		1-((S)-1 Fluoro nethyl 2-meti oxy-ethyl)-5-(6-isopropyl 2 nethoxy pyridin 3 yl) 3 6 dimethyl 1H pyrrolo[3,2 b]pyridine	Rf 0.3 (H xane/ Et yl acetate 3/1)	

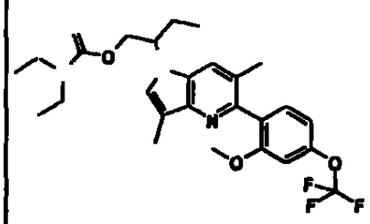
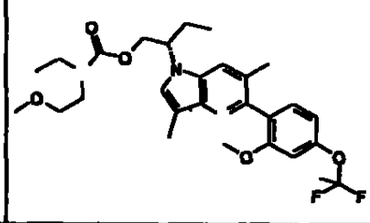
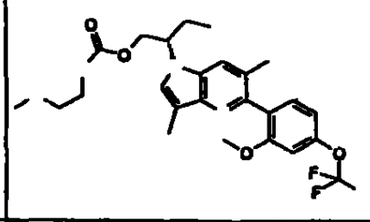
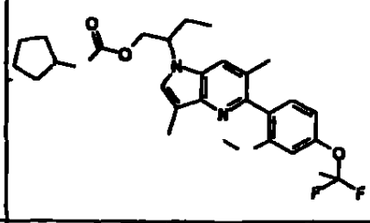
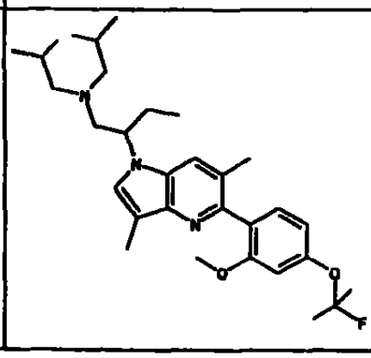
261		{3 [1 ((S)-1 Fl oromethyl 2 methoxy-ethyl)-3 6 dimethyl 1H pyrrolo[3 2 -b]pyridin 5 yl]-6- isopropyl pyridin 2 yl} methyl am ne	Rf 0 3 (Hexane/ Ethyl acetate 2 5/1)	
262		6-Ethyl 1 isopropyl 5 (6 isopropyl 2 methoxy pyridin 3 yl)- 3 m thyl 1H pyrrolo[3 2 b]pyr d ne	352 4	
263		[3-(6 Ethyl 1 isopropyl 3 methyl 1H pyrrol [3 2 b]pyrid 5 yl) 6 sopropyl pyrid 2 yl] m thyl amm e	351 4	
264		6 Ethyl 5 (2-ethyl 6 isopropyl pyrid n 3 yl)- 1 isopropyl 3 methyl 1H pyrrolo[3 2 b]pyr dine	350 4	
265		5-(2 Ethyl 6 sopropyl py di 3 yl)-1-(2 methoxy 1 methoxymethyl-ethyl)- 3 6-dimethyl 1H pyrrolo[3 2 b]py id ne	396 5	

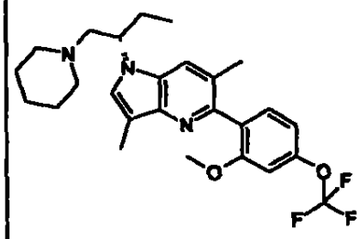
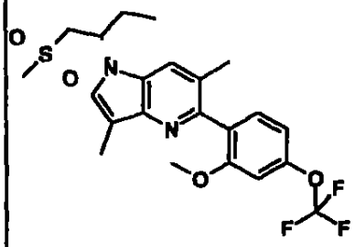
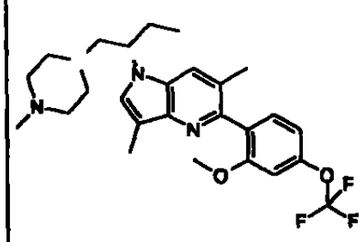
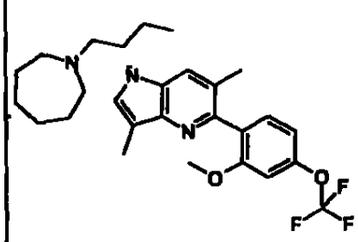
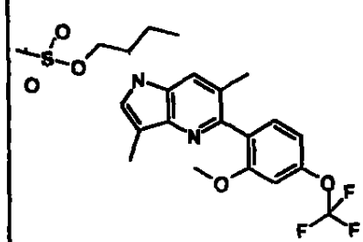
266		{3 [1-((S)-1 Ethoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5-yl]-6-isopropyl pyridin 2 yl} methyl amine	395 5	
267		2 5 Diethyl 6 [1-(1 ethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyr din 5 yl] 3 isopropyl 3H imidazo[4 5 b]pyridine	432 21	2 32
268		(S)-2 [5-(2 M thoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3 2 b]pyridu 1 yl] butan-1-ol	409 3	
269		1-((S)-1 Methoxymethyl propyl)-5-(2 methoxy 4-trifluorometho y phenyl)-3 6-d methyl 1H pyrrolo[3 2 b]pyridine	423 3	
270		1-((S)-1-Chlorom thyl propyl)-5-(2 methoxy 4 tr fluoromethoxy phenyl)- 3 6-d methyl 1H pyrrolo[3,2 b]pyridine	427 4	

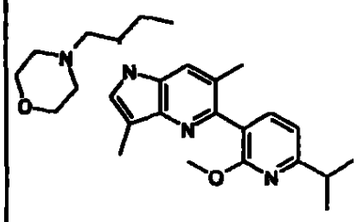
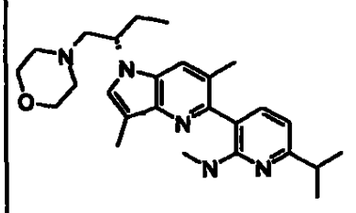
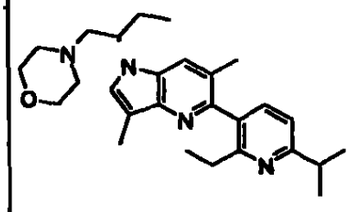
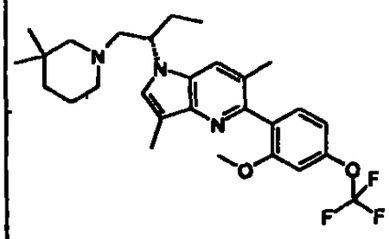
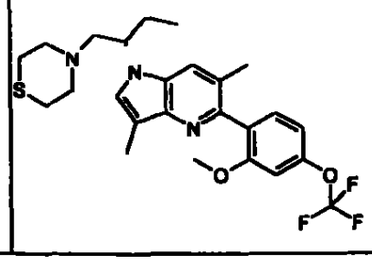
271		1-((S)-2 Methoxy 1 methyl-ethyl)-5-(2 methoxy-4 trifl oromethoxy phenyl)-3 6-dim thyl 1H pyrrolo[3 2 b]pyridine	409 4	
272		5 (2 Methoxy-4 trifl oromethoxy phenyl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyridine	337 1	
7		5-(2 Methoxy-4 trifluoromethoxy ph yl) 3 6-d methyl 1-((S) 1 morphol n-4 ylmethyl propyl)-1H pyrrolo[3 2 b]pyridine	478 06	1 91
274		{(S)-2 [5-(2 Methoxy 4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] butyl}-dimethyl amine	436 04	1 84
275		5 (2 Methoxy-4 trifluoromethoxy phe yl)-3 6-dimethyl 1-((S) 1 pyrrolidin 1 ylmethyl propyl) 1H pyrrol [3 2 b]pyrid ne	462 4	

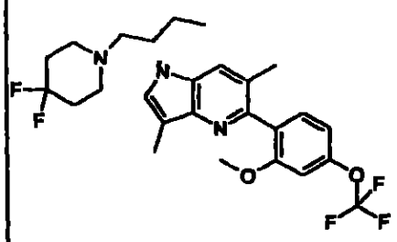
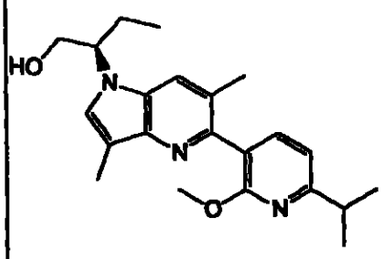
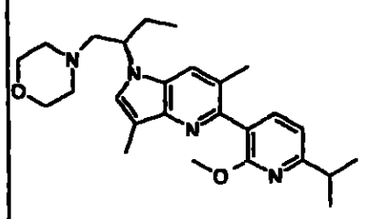
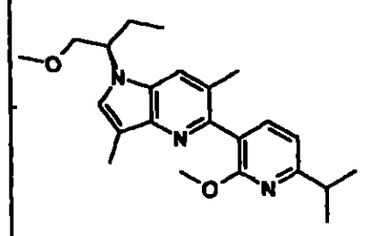
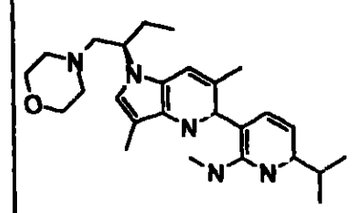
276		(S)-2 [5-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] butan 1-ol	368 3	
277		5 (6-Isopropyl 2 methoxy-pyridin 3 yl)-1 ((S)-1 methoxymethyl propyl)- 3 6-dimethyl 1H pyrrolo[3,2 b]py idine	382.3	
278		M thanesulfonic acid (S) 2 [5-(6-isopropyl 2-methoxy pyr din 3 yl)-3 6-d meti yl pyrrolo[3 2 b]pyridi 1 yl] b tyl ester	446 04	2 23
279		{(S)-2 [5-(6-Isopropyl 2 n thoxy pyridin 3 yl) 3 6-dim thyl- pyrrolo[3,2 b]pyr di 1 yl] butyl}-dim thyl amine	395 13	1 87
280		(2R,6S)-2 6-Dim thyl morpholine-4 carboxylic ac d 2 [5 (2 m thoxy-4 trifluoromethoxy phe yl) 3 6-dim thyl pyrrolo[3,2 b]pyridin 1 yl] butyl ester	550 1	2 31

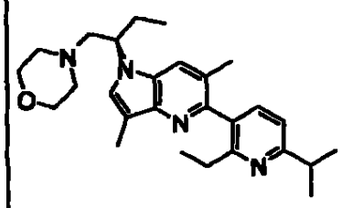
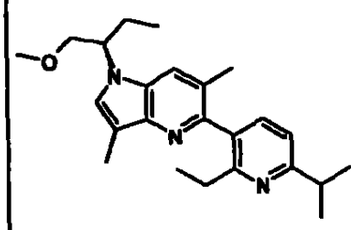
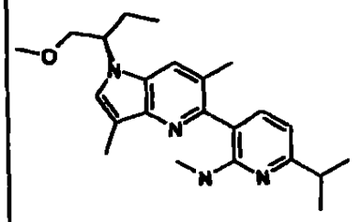
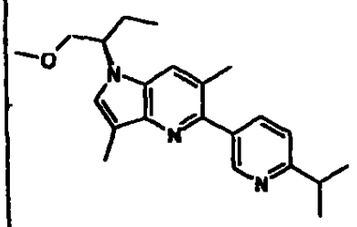
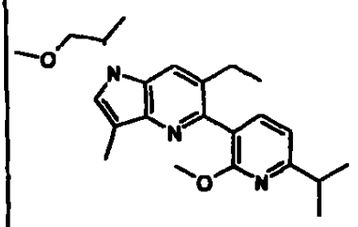
281		Piperidine 1-carboxylic acid (S)-2 [5-(2 methoxy-4-trifluoromethoxy phenyl) 3 6-d methyl pyrrolo[3 2 b]pyridin 1 yl] butyl ester	520 11	2 36
282		4-Methyl piperazine 1 carboxylic ac d (S)-2 [5-(2 methoxy-4 trifluoromeths xy phenyl) 3 6-d methyl pyrrolo[3 2 b]py idi 1 yl] butyl ester	535 13	1 25
283		Azepane 1-carboxylic acid (S)-2 [5 (2 methoxy-4 trifl oromethо y phenyl)-3 6-d methyl pyrrol [3 2 b]pyridi 1 yl] butyl ester	534 13	1 45
284		4 Acetyl p perazi e 1 carboxyl c ac d (S)-2 [5-(2 metho y-4 trifl oromethoxy phenyl)-3 6-d methyl pyrrolo[3,2 b]pyrid n 1 yl] butyl ester	563 12	1 35
285		Ethyl methyl-ca bamic acid (S)-2 [5 (2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyrid 1 yl] butyl ester	494 10	1 40

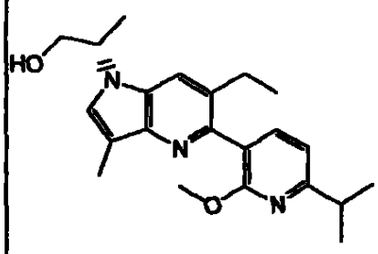
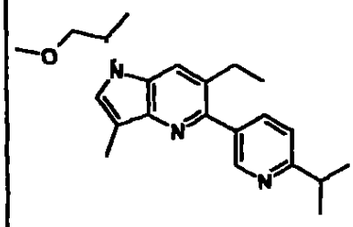
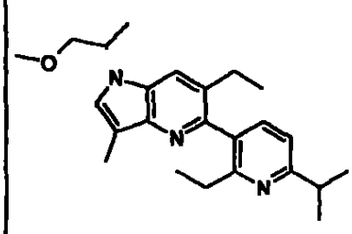
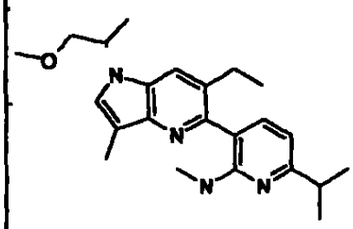
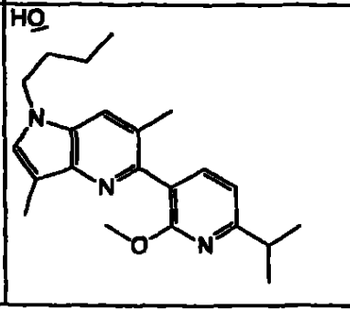
286		Diethyl-carbamic acid (S) 2-[5-(2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] butyl ester	508 12	1 41
287		Ethyl-(2 methoxy ethyl)-carbamic acid (S) 2 [5-(2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl] butyl ester	538 12	1 41
288		(2 Methoxy-ethyl)-carbamic acid (S)-2 [5 (2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] butyl ester	510 09	2 18
289		Cyclopentyl-carbamic acid (S)-2 [5-(2 methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] butyl ester	520 12	1 43
290		1 [(S) 1-((2S 6R) 2 6-Dimethyl morpholin-4 ylmethyl)-propyl] 5-(2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl 1H pyrrol [3,2 b]pyridine	506 13	1 30

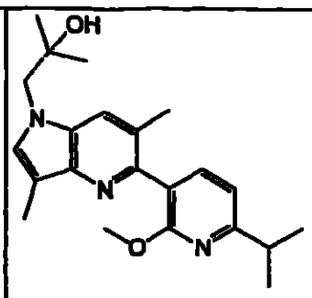
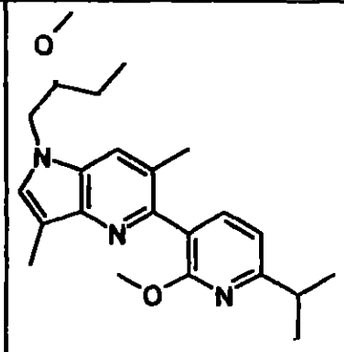
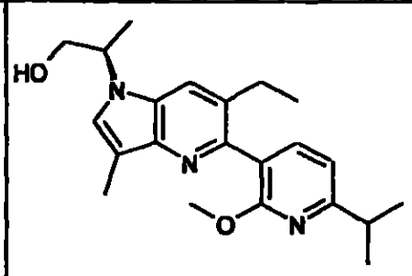
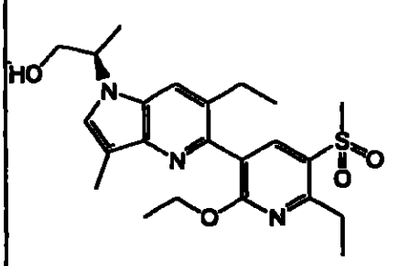
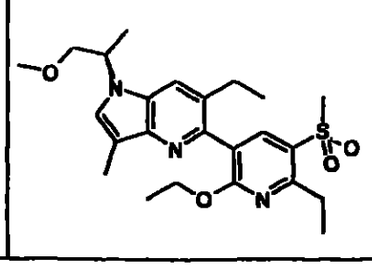
291		5-(2 Methoxy-4 trifl romethoxy phenyl)-3 6-d methyl 1 ((S) 1 piperid n 1 ylm thyl propyl) 1H pyrrolo[3 2 b]pyridine	476 13	1 85
292		1-((S)-1 Methanes lf nylmethyl -propyl)-5 (2 methoxy 4 trifluoromethoxy phe yl) 3 6-d methyl 1H pyrrolo[3 2 b]pyridine	471 03	2 11
293		5 (2 Methoxy-4 t fl orom th xy phenyl) 3 6-dimethyl 1 [(S) 1 (4 methyl p perazin 1 ylmethyl)- propyl] 1H pyrrolo[3 2 b]py dine	491 13	1 84
294		1-((S) 1 Azepan 1 ylmethyl propyl) 5-(? methoxy-4 trifluoromethoxy- phenyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyrid ne	490 14	1 89
295		Methanesulfo ic ac d (S)-2 [5-(2 methoxy-4 trifluoromethoxy phenyl) 3 6-dimethyl pyrrolo[3 2 b]pyrid n 1 yl] bi tyl e ter	487 04	2 16

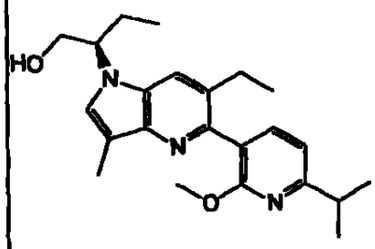
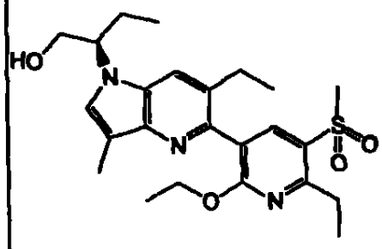
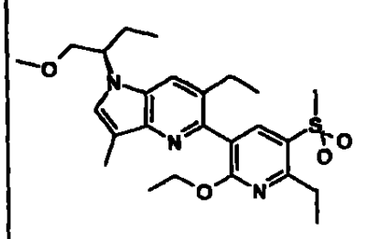
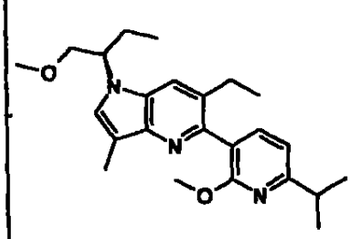
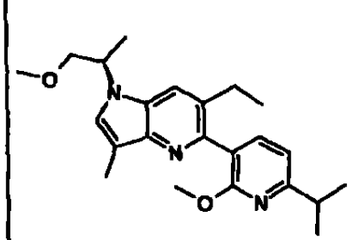
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297		{3 [3 6-Dimethyl 1 ((S)-1 morpholin-4-ylmethyl propyl)-1H pyrrolo[3 2 b]py id n 5 yl]-6 isopropyl pyridin 2 yl}-methyl-amin	436 19	1 57
298		5-(2 Ethyl-6 isopropyl pyridin 3 yl)-3 6-dimeth yl 1-((S)-1 morphol -4 ylmeth yl propyl)-1H pyrrolo[3,2 b]py idine	435 20	1 57
299		1 [(S)-1-(3 3 Dimethyl p p idin 1 ylmethyl)-propyl] 5-(2 ethoxy 4-trifluoromethoxy phenyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	504 5	
300		5 (2 Methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl 1-((S) 1 thiomorpholin 4-ylmethyl propyl)-1H pyrrolo[3,2 b]pyridin	494 07	1 97

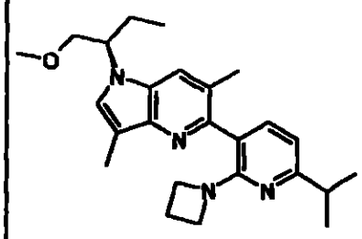
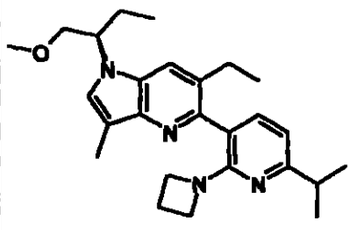
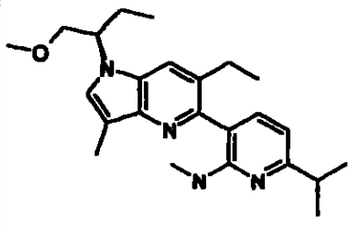
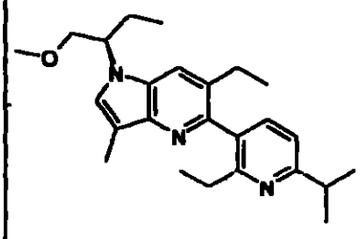
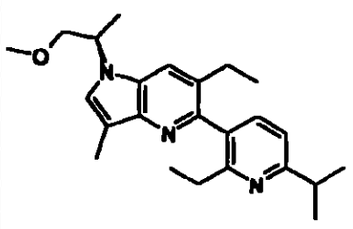
301		1 [(S)-1-(4 4 Diflu ro-p pe d 1 ylmethyl) propyl] 5 (2-m tho y 4-trifluoromethoxy phenyl)-3 6-d methyl 1H pyrrolo[3 2 b]pyrid ne	512 10	2 13
302		(R)-2 [5-(6-Isopropyl 2-methoxy pyrid 3 yl)-3 6-d methyl pyrrolo[3 2 b]pyrid n 1 yl] buta 1-ol	368 16	2 21
303		5-(6 Isopropyl 2 meth xy pyrid n 3 yl)-3 6-dimethyl 1-((R) 1 morph l n-4-ylmethyl propyl)-1H pyrrolo[3 2 b]pyrid e	437 16	1 95
304		5-(6-Isopropyl 2 methoxy pyr d 3 yl)-1-((R) 1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	382 16	2 28
305		{3 [3 6 Dimethyl 1 ((R)-1 morpholin-4 ylmethyl propyl) 1H pyrrolo[3,2 b]pyrid n 5 yl]-6-i opropyl pyr d 2 yl} methyl amine	436 16	1 58

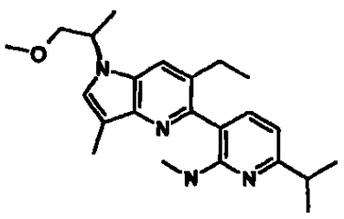
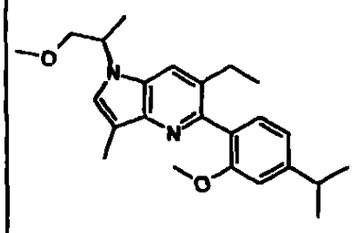
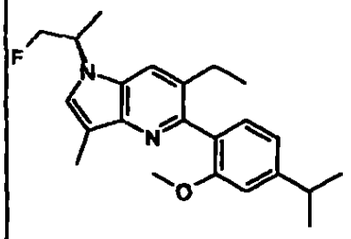
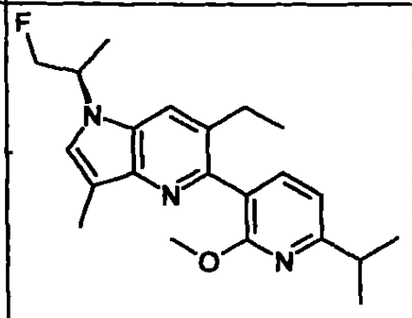
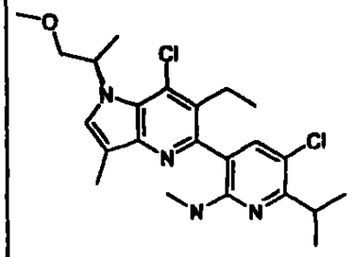
306		5-(2 Ethyl-6-isopropyl pyridin 3 yl)-3 6-dimethyl 1-((R)-1 morpholin-4 ylmethyl propyl)-1H pyrrolo[3,2 b]pyridine	435 15	1 59
307		5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1-((R)-1 methoxymethyl propyl) 3 6-d methyl-1H pyrrolo[3,2 b]pyrid i	380 5	
308		{6-Isopropyl 3 [1-((R)-1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyrid 5 yl] py din-2 yl} methyl-amine	381 17	1 89
309		5-(6 Isopropyl pyridin 3 yl)-1 ((R)-1 n ethoxymethyl propyl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyrid ne	352 4	
310		6-Ethyl 5-(6- sopropyl 2 m thoxy pyrid n 3 yl)-1-((S) 2 m thoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]py id ne	382 19	2 31

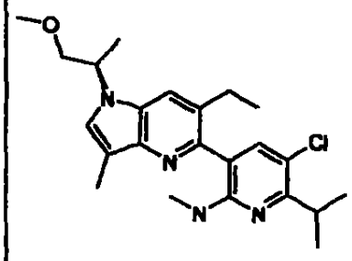
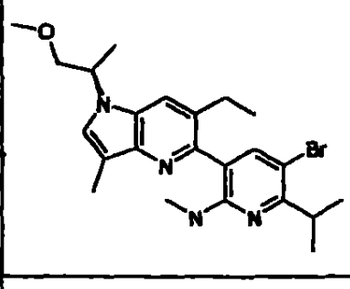
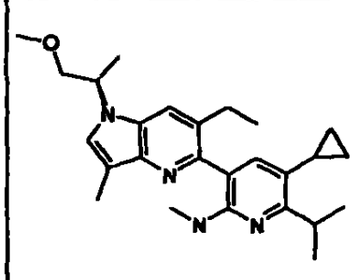
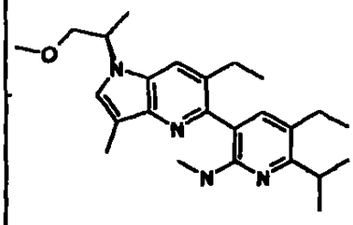
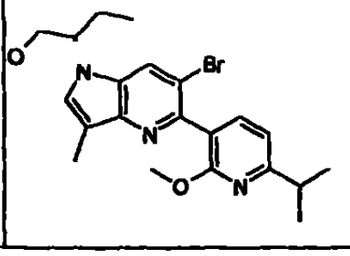
311		(S)-2 [6-Ethyl 5-(6-isopropyl 2-m thoxy pyrid 3 yl)-3-methyl pyrrolo[3 2 b]pyridin 1 yl] propa 1-ol	368 3	
312		6 Ethyl 5-(6-isopropyl pyridin 3 yl)-1 ((S)-2 methoxy 1 methyl ethyl)- 3 methyl 1H pyrrolo[3 2 b]pyr d n	352 18	2 03
313		6-Ethyl 5-(2-ethyl-6 i opropyl pyrid 3 yl)-1 ((S)-2 m thoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid ne	380 20	2 08
314		{3 [6-Ethyl 1-((S) 2 methoxy 1 methyl ethyl) 3 methyl-1H pyrrolo[3,2 b]pyridin 5 yl] 6 isopropyl pyridin-2 yl} methyl amine	381 19	1 90
315		(R)-1 [5-(6 Isopropyl 2 m thoxy pyrid n 3 yl) 3 6-dimethyl pyrrolo[3 2 b]pyrid n 1 yl] b t n 2-ol	368 36	2 16

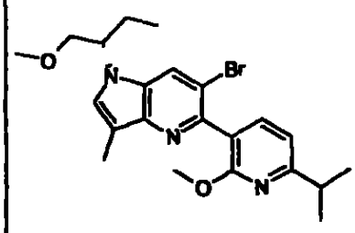
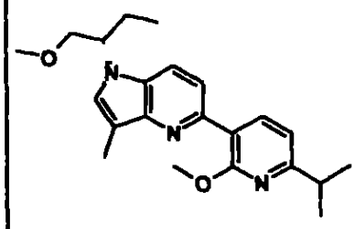
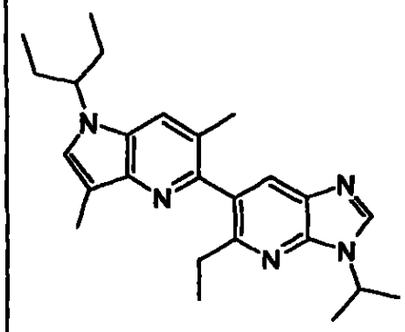
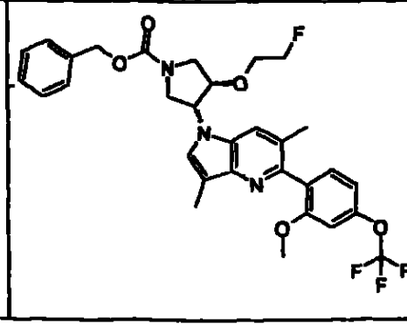
316		1 [5-(6 Isopropyl 2 methoxy pyr d n 3 yl) 3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] 2 methyl propan 2-ol	368 37	2 18
317		5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-((R)-2 methoxy butyl)-3 6-dimethyl 1H pyrrolo[3,2 b]py dine	382 32	2 30
318		(R)-2 [6-Ethyl 5 (6-isopropyl 2 methoxy pyridin 3 yl)-3 thyl pyrrolo[3 2 b]pyridin 1 yl] propa 1-ol	368 4	
319		(R) 2 [5-(2 Ethoxy-6 ethyl 5 methanes lfonyl pyrid i 3 yl)-6-ethyl 3 methyl pyrrolo[3,2 b]pyr din 1 yl] propan 1-ol	446 35	2 04
320		5-(2 Ethoxy-6-ethyl 5 metha nesulfo yl pyridi 3 yl)-6-ethyl 1 ((R) 2 methoxy 1 methyl-ethyl) 3 methyl 1H pyrrolo[3 2 b]pyridine	460 32	2 19

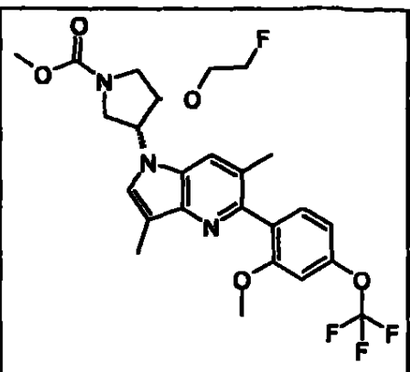
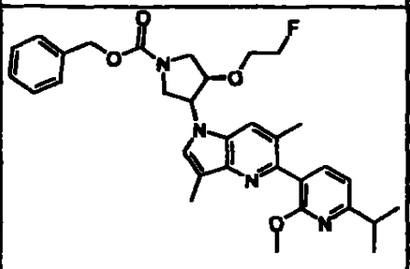
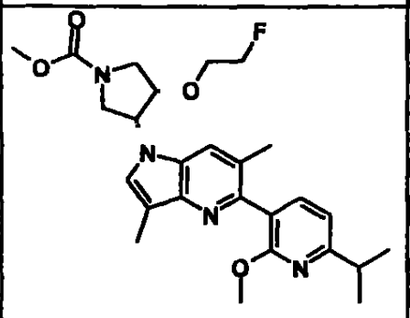
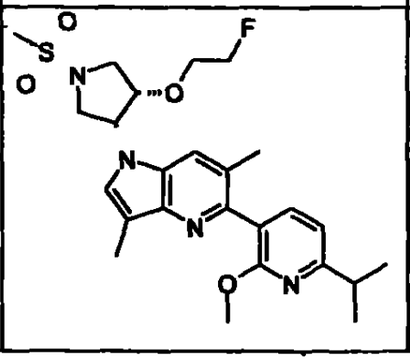
321		(R) 2 [6 Ethyl 5-(6-isopropyl 2 m thoxy pyrid n 3 yl)-3 methyl pyrrolo[3,2 b]pyridin 1 yl] butan 1-ol	382 43	2 26
323		(R)-2 [5-(2 Ethoxy-6-ethyl 5 methanesulfonyl pyridin 3 yl)-6-ethyl-3 methyl pyrrolo[3 2 b]pyrid n 1 yl] b tan 1-ol	460 16	1.37
324		5 (2 Ethoxy-6-ethyl 5 meth es lfonyl pyridin-3 yl)-6-ethyl 1 ((R) 1 m thoxym thyl propyl) methyl 1H pyrrolo[3 2 b]pyrid	474 19	1 42
325		6-Ethyl 5-(6- sopropyl 2 methoxy-py ridin 3 yl)-1 ((R)-1 methoxymethyl propyl)-3 methyl 1H pyrrolo[3 2 b]p yridine	396 42	2 35
326		6 Ethyl 5 (6 isopropyl 2 methoxy py idin 3 yl)-1-((R) 2 methoxy 1 methyl-ethyl)-3 m thyl 1H pyrrolo[3 2 b]pyrid ne	382 44	2 29

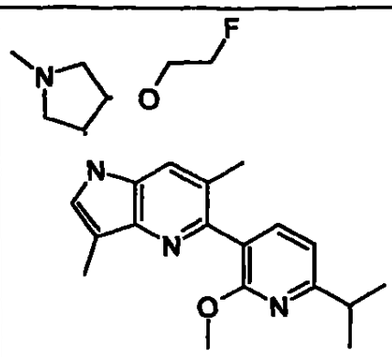
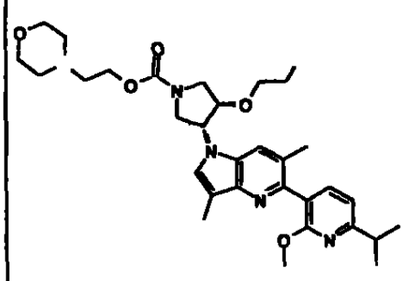
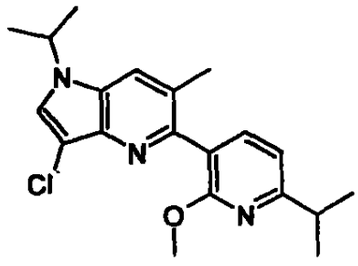
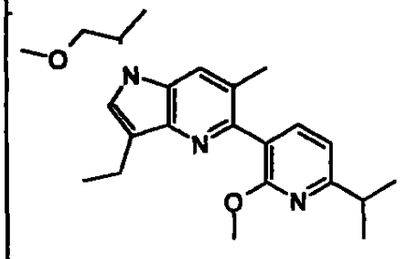
327		5-(2 Azetidin 1 yl-6-isopropyl pyridin 3 yl)-1-((R)-1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	407 43	2 02
328		5-(2 Azetidin 1 yl-6 isopropyl pyridin 3 yl)-6-ethyl-1-((R)-1 methoxymethyl propyl)-3 methyl 1H pyrrolo[3,2 b]pyridine	421 44	2 13
329		{3 [6-Ethyl 1 ((R)-1 methoxymethyl propyl)-3 methyl 1H pyrrolo[3,2-b]pyridin 5 yl]-6-isopropyl pyridin 2 yl} m thyl amine	395 45	1 99
330		6-Ethyl-5-(2-ethyl-6-isopropyl pyridin-3 yl)-1-((R)-1 methoxymethyl propyl)-3 methyl 1H pyrrol [3,2 b]pyridine	394 45	2 14
331		6-Ethyl 5-(2-ethyl-6 isopropyl pyridin 3 yl)-1-((R)-2 methoxy 1 methyl-ethyl) 3 methyl 1H pyrrolo[3 2 b]pyr dine	380 45	2 07

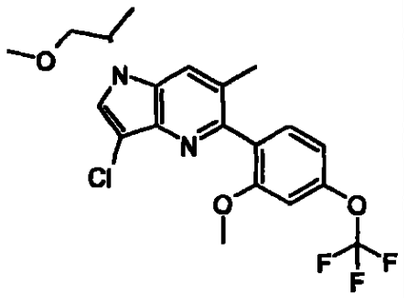
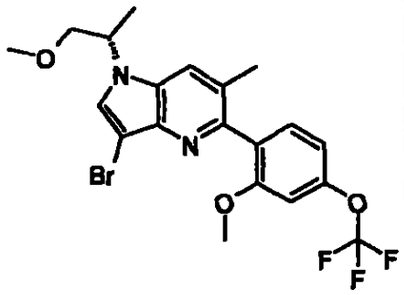
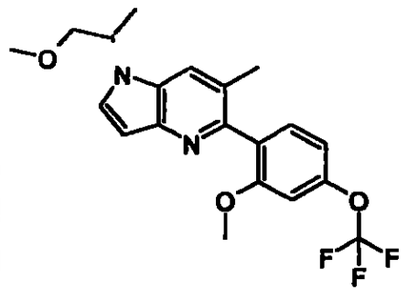
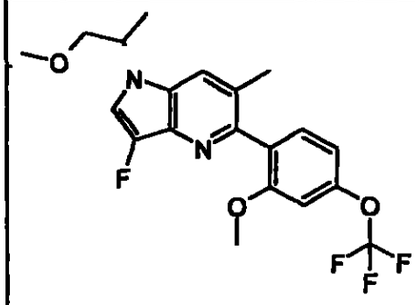
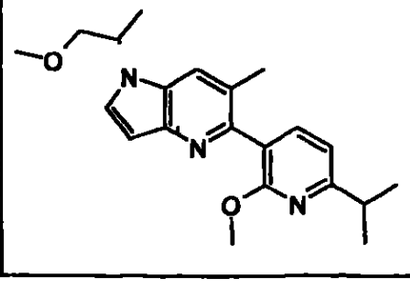
332		{3 [6-Ethyl 1 ((R)-2 m thoxy 1 methyl ethyl) 3 m thyl 1H pyrrolo[3 2 b]pyr d n 5 yl]-6- sopropyl pyrıdın 2 yl} methyl am ne	381 45	1 88
3 3 4		6 Fthyl 5-(4 ısopropyl 2 methoxy phenyl) 1 ((R)-2 methoxy 1 methyl-ethyl) 3 methyl 1H pyrrolo[3 2 b]pyrıd ne	381 47	2 30
334		6-Fthyl 1 ((R) 2 fl ro-1 m thyl-ethyl)-5 (4 ısopropyl 2 methoxy ph nyl)-3 methyl 1H pyrrolo[3 2 b]pyrıd ne	369 46	2 28
335		6 Ethyl 1-((R) 2 fluoro-1 methyl-ethyl)-5-(6-ısopropyl 2 methoxy pyrıdın 3 yl)-3 methyl 1H pyrrolo[3 2 b]py ıdine	370 45	2 31
336		{5 Chloro-3 [7-chloro 6-ethyl 1-((R) 2 methoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrıdı 5 yl]-6 ısopropyl pyr dın 2 yl} methyl am ne	449 33/ 451 33	2 91

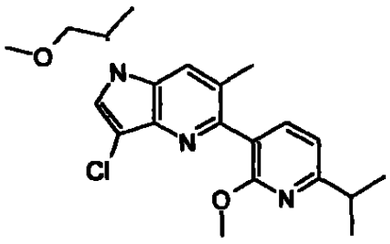
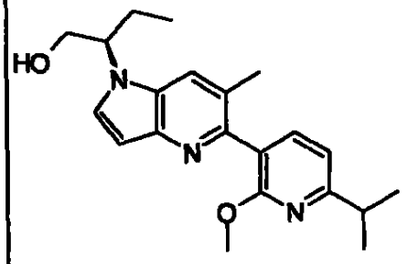
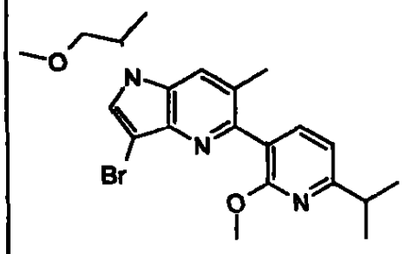
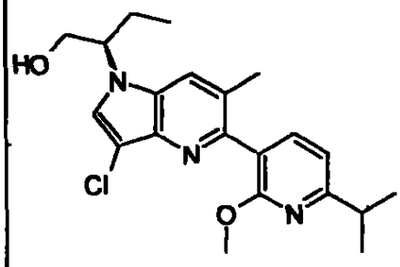
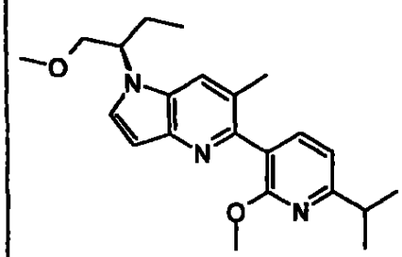
337		{5-Chloro-3 [6-ethyl 1 ((R)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl-pyr din 2 yl}-m thyl-amine	415 40/ 417 39	2 53
338		{5 Bromo-3 [6-ethyl 1 ((R)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyrid n 5 yl]-6-isopropyl pyridin 2 yl}-methyl-am ne	459 35/ 461 35	2 55
339		{5-Cy lopropyl 3 [6 ethyl 1-((R)-2 methoxy 1-methyl ethyl) 3 methyl 1H py rolo[3 2 b]py id n 5 yl]-6 isopropyl pyridin 2 yl} m thyl amine	421 47	2 38
340		{5 Ethyl 3 [6-ethyl 1 ((R) 2 nethoxy 1 methyl-ethyl)-3 methyl 1H pyrrol [3 2 b]pyrid 5 yl]-6 isopropyl-pyridin 2 yl} methyl-amin	409 49	2 29
341		(S)-2 [6 Bromo-5-(6 isopropyl 2-m thoxy pyrid n 3 yl)-3-methyl pyrrolo[3,2 b]pyridin 1 yl] butan 1-ol	431 35/ 433 35	2 62

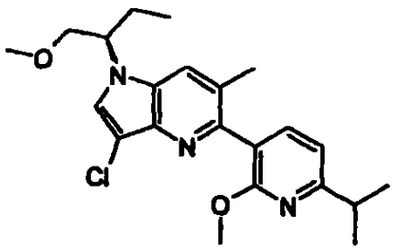
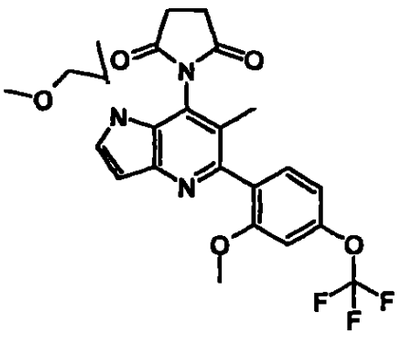
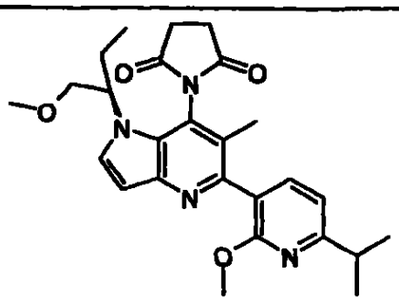
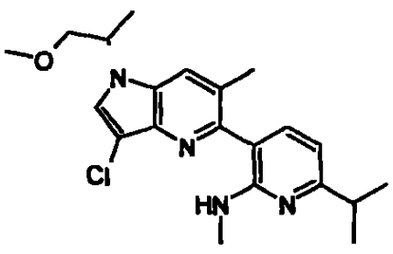
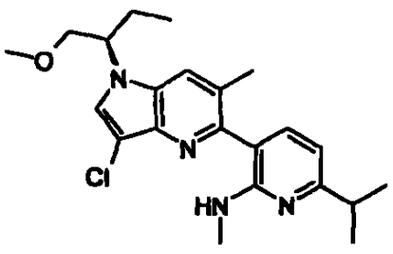
342		6 Bromo 5 (6-isopropyl 2 methoxy pyr d 3 yl)-1 ((S) 1 methoxymethyl propyl)-3 methyl-1H pyrrolo[3 2 b]pyridine	445 38/ 447 37	2 80
343		5-(6 Isopropyl 2 methoxy pyrid n 3 yl) 1-((S)-1 methoxymethyl propyl)- 3 methyl 1H pyrrolo[3 2 b]pyrid n	367 15	2 22
344		5 Ethyl 6-[1 (1-ethyl propyl)-3 6-dim thyl 1H pyrrolo[3,2 b]pyridin 5 yl] 3 isopropyl 3H im d zo[4 5 b]pyrid n	404 33	1 44
345		(3S 4R) 3-(2 Fluoro ethoxy)-4-[5-(2 methoxy-4-trifluoromethoxy phenyl) -3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl]-pyrrolidine-1 carboxyl c ac d be zyl ester	602 06	1 47

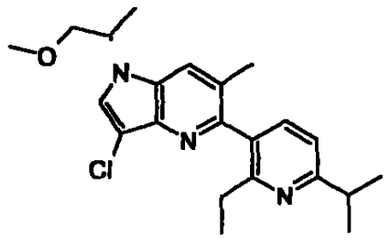
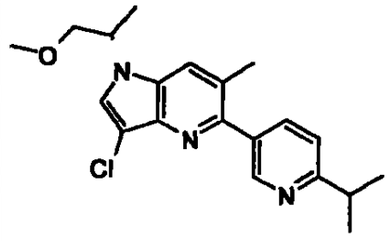
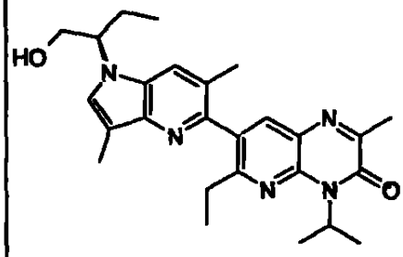
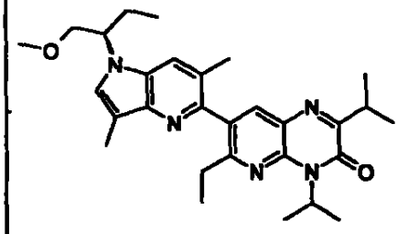
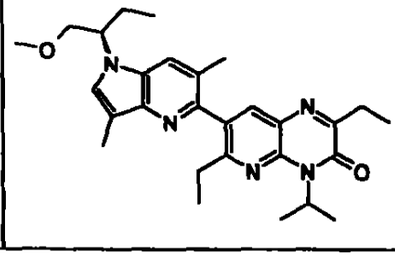
346		(3S 4R)-3-(2 Fluoro-ethoxy)-4-[5-(2 methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl] pyrrolidine-1 carboxylic acid m th yl ester	526 02	1 35
347		(3S 4R)-3-(2 Fluoro-ethoxy)-4-[5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-d nethyl pyrrolo[3,2 b]py d 1 yl] pyrrolidine-1 carboxylic acid benzyl ester	561 11	1 49
348		(3S 4R) 3 (2 Fluoro-ethoxy)-4 [5-(6-isopropyl 2 nethoxy pyridi 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl] pyrrolidine-1 carboxylic acid methyl ester	485 13	1 39
349		1 [(3R,4S)-4 (2 Fluoro-ethoxy)-1 methanesulfo yl pyrrolidin 3 yl] 5-(6-isopropyl 2 methoxy pyridin 3 yl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridin	505 10	1 35

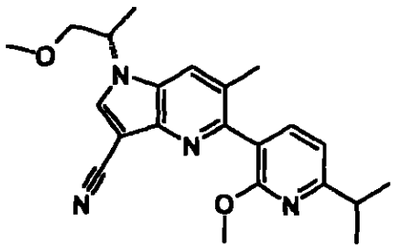
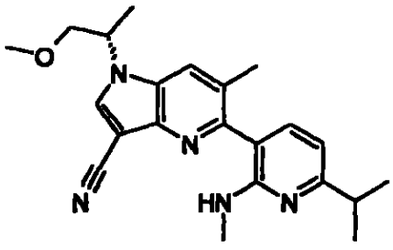
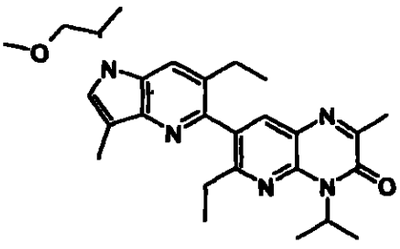
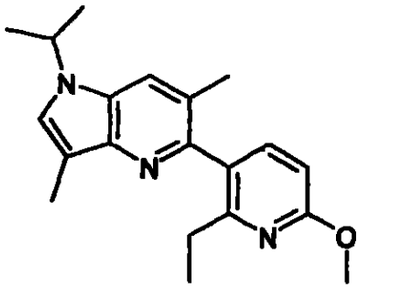
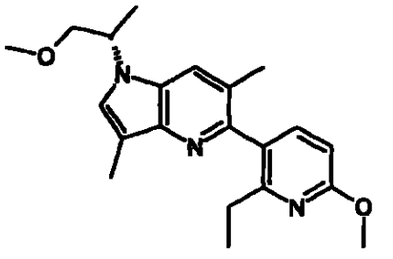
350		1 [(3R 4S)-4-(2 Fl oro eth xy)-1 methyl pyrrol dın 3 yl] 5-(6 isopropyl 2 meth xy pyrıdın 3 yl) 3 6-d methyl 1H pyrrolo[3 2 b]pyrıd	441 14	1 24
351		(3S 4R)-3-(2 Fluoro-etho y)-4 [5-(6-isopropyl 2 methoxy pyr d 3 yl)-3 6-dımethyl pyrrolo[3 2 b]pyrıd n 1 yl] pyrrolıdıne 1 carboxyl c ac d 2 morpholı -4 yl-ethyl este	584	1 38
352		3 Chloro-1 ısopropyl 5-(6-ısopropyl 2 methoxy pyrıdın 3 yl)-6-methyl 1H pyrrol [3 2 b]py ıd ne	358 09 360 08	1 60
353		3 Ethyl 5-(6-ısopropyl 2-methoxy pyrıdı 3 yl) 1-((S) 2 methoxy 1-methyl-ethyl)-6-methyl 1H pyrrolo[3 2 b]pyrıdıne	382 19	1 44

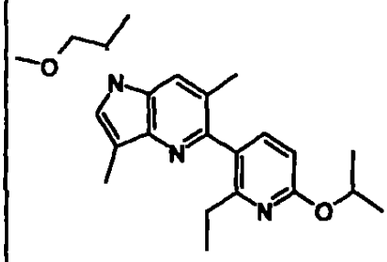
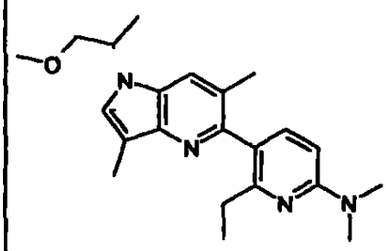
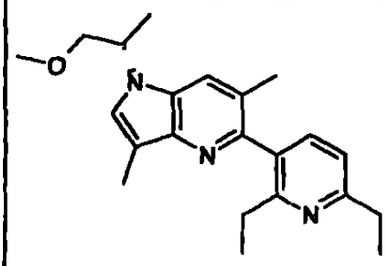
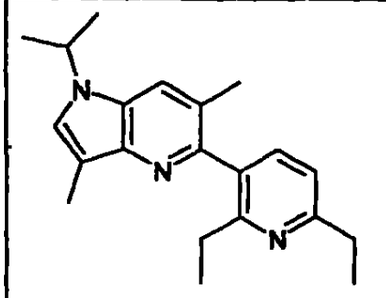
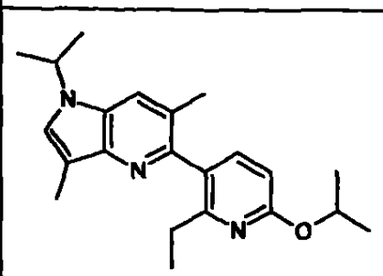
354		3-Chloro-1-((S) 2 methoxy-1-methyl ethyl)-5-(2 methoxy-4 trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2 -b]pyrid ne	429 02 431 02	1 53
355		3 Bromo-1-((S)-2 methoxy 1 methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2 b]pyridine	472 96 474 96	1 54
356		1-((S)-2 Methoxy 1 methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2 b]pyridin	395 04	1 34
357		3 Fluoro-1-((S)-2 methoxy 1 methyl ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2 -b]pyridin	413 02	1 49
358		5-(6-Isopropyl 2 methoxy pyridin 3 yl)-1-((S)-2 methoxy 1 methyl ethyl)-6-methyl ethyl 1H pyrrolo[3 2 b]pyrid ne	354 15	1 40

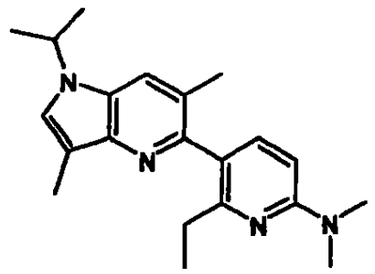
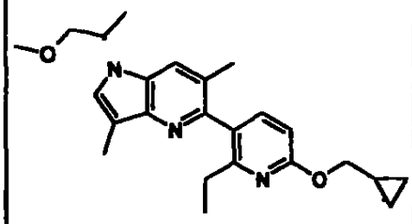
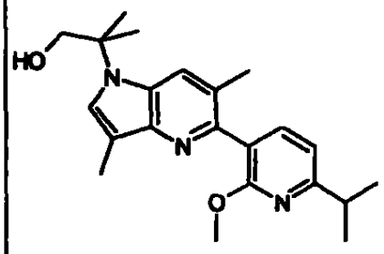
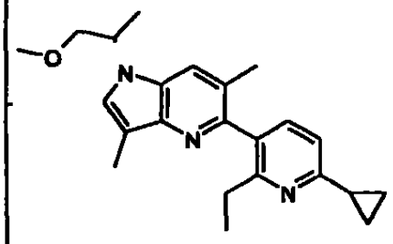
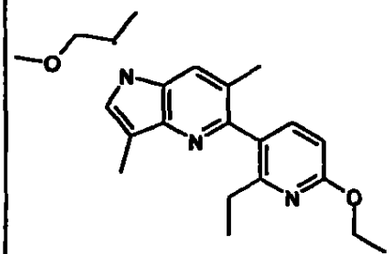
359		3-Chloro 5-(6-isopropyl 2 methoxy pyridin 3 yl)-1-((S)-2 methoxy 1 methyl ethyl)-6-methyl 1H pyrrolo[3 2 b]pyrid n	388 10 390 10	1 56
360		(R)-2 [5-(6 Isopropyl 2 methoxy pyridin 3 yl)-6 methyl pyrrolo[3 2 b]py d 1 yl] buta 1-ol	354 12	1 39
361		3 Bromo 5-(6-isopropyl 2 methoxy pyridi 3 yl)-1 ((S) 2 m thoxy 1 methyl ethyl)-6 methyl 1H pyrrolo[3 2 b]pyridine	432 4 4	1 59
362		(R)-2 [3-Chloro-5 (6 isopropyl 2 methoxy pyridin 3 yl)-6 methyl pyrrolo[3 2 b]pyridin 1 yl] b tan 1-ol	388 10 390 10	1 56
363		5-(6 Isopropyl 2 methoxy pyrid n 3 yl)-1-((R) 1 methoxymethyl propyl) 6-methyl 1H pyrrolo[3 2 b]pyrid ne	368 26	1 44

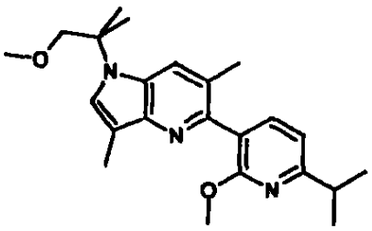
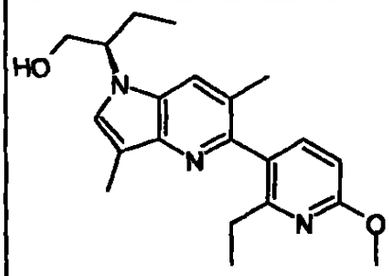
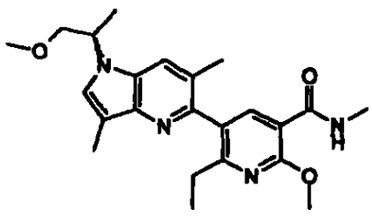
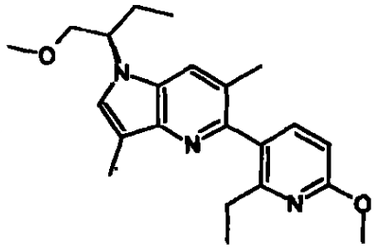
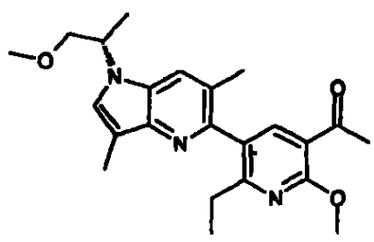
364		3-Chloro-5 (6-isopropyl 2 m thoxy pyridin 3 yl)-1-((R)-1 methoxymethyl propyl)-6-methyl-1H pyrrolo[3,2-b]pyrid n	402 404	1 62
365		1 [1-((S)-2 Methoxy 1 methyl-ethyl)-5-(2 methoxy-4 trifluoromethoxy phenyl)-6-methyl-1H pyrrolo[3,2-b]pyrid n 7 yl] pyrrolidine-2 5 di ne	492 09	1 38
366		1 [5-(6-Isopropyl 2 methoxy-pyr d n 3 yl)-1-((R)-1 methoxy ethyl propyl)-6 methyl 1H pyrrolo[3 2 b]pyrid 1 7 yl]-pyrrolidine-2 5 dione	465 21	1 48
367		{3 [3-Chloro-1-((S)-2 methoxy 1 methyl-ethyl)-6- ethyl 1H pyrrolo[3,2 b]py idin 5 yl]-6-isopropyl pyr din 2 yl} methyl-amine	387 389	1 32
368		{3 [3-Chloro 1-((R)-1 m thoxymeth yl propyl)-6 m thyl 1H pyrrolo[3,2 b] pyr din 5 yl]-6 isopropyl-pyridin 2 yl} nethyl-amin	401 21 403 20	1 35

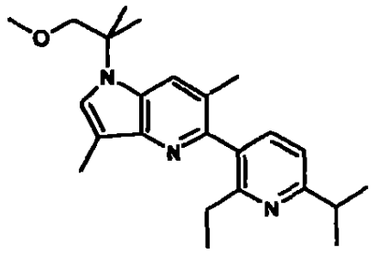
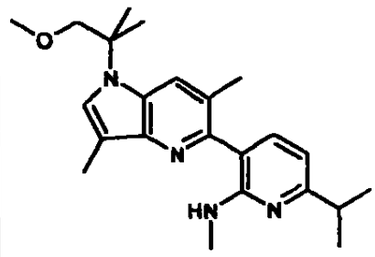
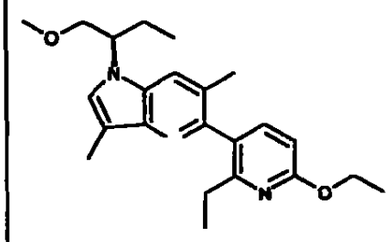
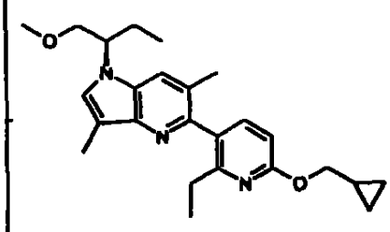
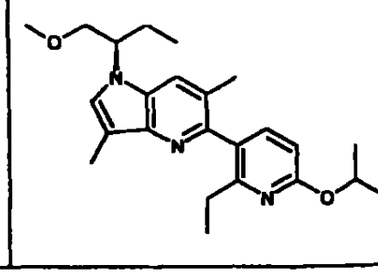
369		3-Chloro-5-(2-ethyl 6-isopropyl pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-6 methyl 1H pyrrol [3 2 b]pyrid	386 19 388 19	1 36
370		3-Chloro-5-(6-isopropyl-pyridin 3 yl)-1 ((S)-2 methoxy 1 methyl-ethyl)-6 methyl 1H pyrrolo[3 2 b]pyridi e	358 14 360 12	1 45
371		6 Ethyl 7 [1 ((R)-1 hydroxymethyl propyl)-3 6-d m thyl 1H pyrrolo[3 2 b]pyr d 5 yl] 4 isopropyl 2 methyl-4H pyrido[2 3 b]pyraz n 3 one	448 23	1 40
372		6-Ethyl 2 4 d isopropyl 7 [1-((R)-1 methoxymethyl propyl)-3 6-d methyl 1H pyrrolo[3 2 b]pyr din 5 yl]-4H pyrido[2 3 b]pyraz n 3 one	490 31	1 53
373		2 6 Diethyl-4 isopropyl 7 [1-((R) 1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl]-4H pyrido[2 3 b]pyrazin 3 one	476 29	1 48

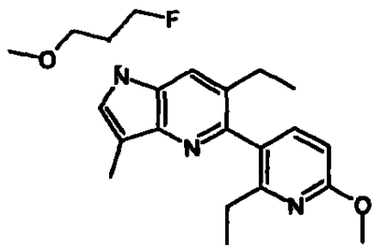
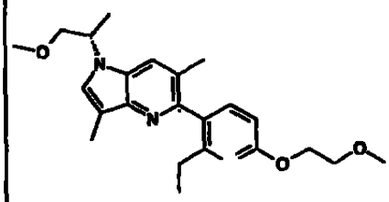
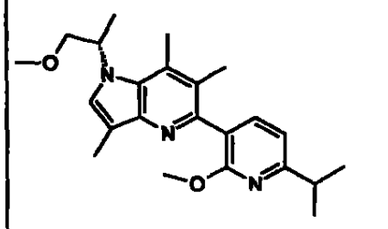
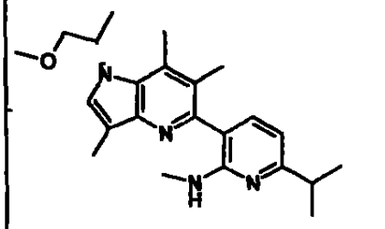
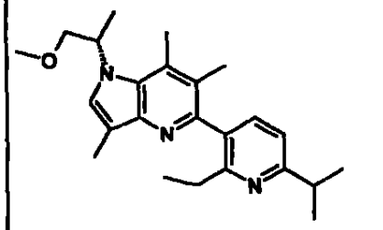
374		5-(6-Isopropyl 2 methoxy pyridin-3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-6 methyl 1H pyrrolo[3 2 b]pyridine-3 carbonitr le	379 19	1 59
375		5-(6-Isopropyl 2 methylamino-pyr din 3-yl)-1-((S)-2 methoxy 1-methyl-ethyl)-6-methyl 1H pyrrolo[3,2 b]pyridine 3 carbonitrile	378.20	1 24
376		6-Ethyl 7 [6- thyl 1 ((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]py idin 5 yl]-4 isopropyl 2-methyl-4H pyrido[2 3 b]pyraz n 3 one	462 27	1 46
377		5-(2 Ethyl-6 methoxy pyridin 3 yl)-1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyridi e	324 40	1 40
378		5-(2 Ethyl-6 m thoxy pyr din 3 yl)-1-((S) 2 methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyrid ne	354 36	1 39

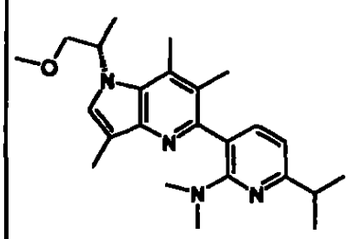
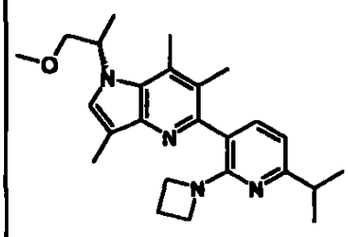
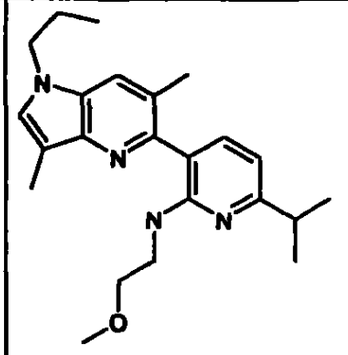
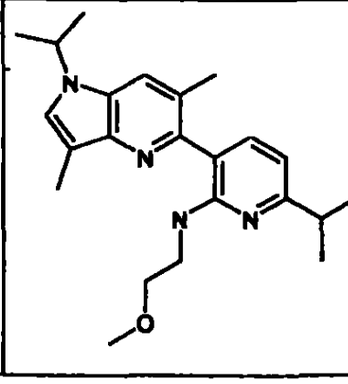
379		5 (2 Ethyl-6 isopropoxy pyrid 3 yl)-1 ((S)-2 meth xy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyridine	382 42	1 52
380		{6 Ethyl 5 [1 ((S)-2 methoxy 1 methyl ethyl) 3 6-d methyl 1H pyrrolo[3 2 b]pyrid n 5 yl] pyridin 2 yl} d methyl-amine	367 43	1 32
381		5 (2 6 D thyl pyrid 3 yl)-1-((S)-2-methoxy-1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyrid	35 45	1 32
382		5-(2,6 D ethyl-pyrid n 3 yl)-1 isopropyl 3 6 dimethyl 1H pyrrolo[3 2 b]py d n	322 45	1 36
383		5-(2 Fthyl-6-isopropoxy pyridin yl) 1 sopropyl 6 dimethyl 1H pyrrol [3 2 b]pyrid n	352 45	1 54

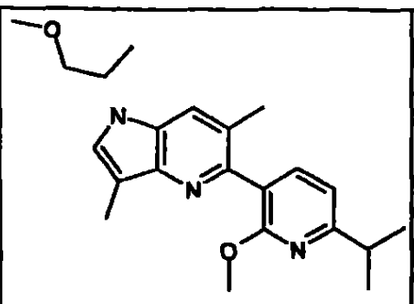
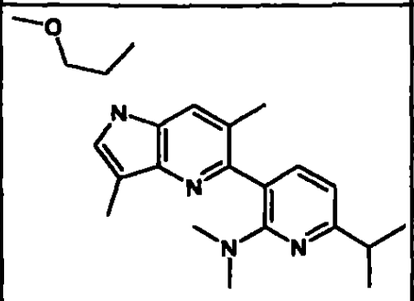
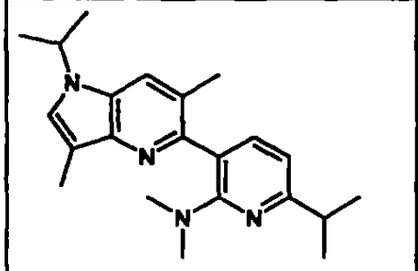
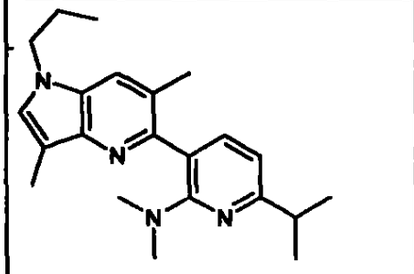
384		[6 Ethyl 5-(1 isopropyl 3 6-dim eth yl 1H pyrrolo[3,2 b]pyridin 5 yl)-pyridin-2 yl]-dimethyl-amine	337 44	1 31
385.		5-(6 Cyclopropylmethoxy 2-ethyl-pyridin 3 yl)-1 ((S)-2 methoxy 1 methy l-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyr din	394 16	1 43
386		2 [5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyr din 1 yl] 2 methyl propan 1-ol	368 44	1 56
387		5-(6-Cy lopropyl 2 ethyl pyridin 3 yl)-1 ((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyr dine	364 45	1 42
388		5-(6-Ethoxy 2-ethyl pyridin 3 yl)-1 ((S)-2 methoxy 1 methyl ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	368 48	1 50

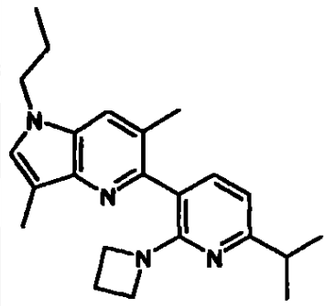
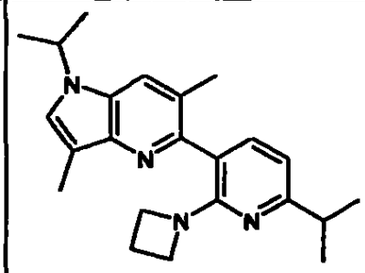
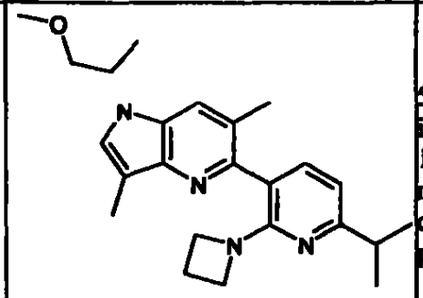
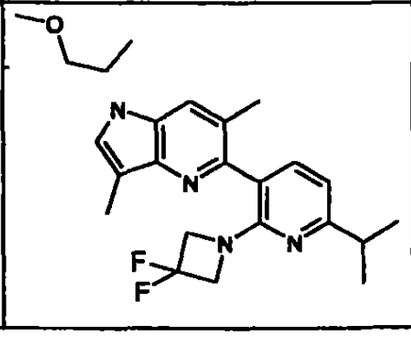
389		5 (6-Isopropyl 2 methoxy py din 3 yl)-1 (2 m thoxy 1 l d methyl ethyl)-3 6-d methyl 1H pyrrolo[3 2 b]pyrid ne	382 53	1 60
390		(R) 2 [5 (2 Ethyl 6 methoxy pyr 1 3 yl)-3 6-d methyl pyrrolo[3 2 b]pyrid 1 yl]-butan 1-ol	354 46	1 49
391		6 Ethyl 2 methoxy 5 [1-((S) 2 m th y 1 methyl ethyl) 3 6 d m thyl 1H pyrrolo[3 2 b]pyridin 5 yl] N methyl nicoti m de	411 41	1 44
392		5-(2 Ethyl 6-methoxy pyridi 3 yl) 1 ((R)-1 methoxym thyl propyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridi e	368 47	1 50
393		1 {6-Ethyl 2 methoxy 5 [1 ((S)-2 methoxy 1 methyl-ethyl)-3 6 dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl] pyrid 3 yl eth	396 43	1 43

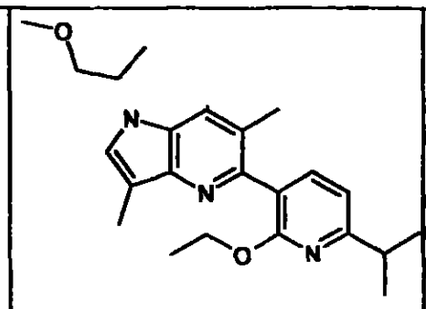
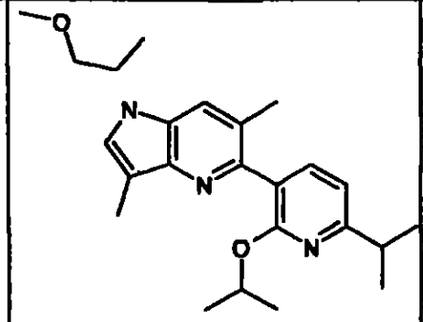
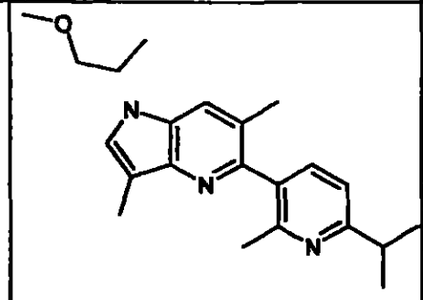
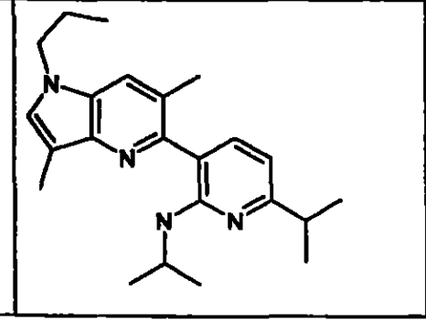
394		5-(2 Ethyl-6-isopropyl pyridin-3 yl)-1-(2 methoxy 1 1-dim thyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridi	380 49	1 41
395		{6-Isopropyl 3 [1-(2 methoxy 1 1-dimethyl ethyl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl] py d 2 yl} methyl-am ne	381 49	1 37
396		5-(6-Ethoxy 2-etl yl pyridin 3 yl)-1 ((R) 1 n ethoxym thyl propyl)-3 6-di nethyl 1H pyrrolo[3,2 b]py idine	382 48	1 49
397		5-(6-Cyclopropylm thoxy 2 etl yl pyr d 3 yl)-1 ((R) 1 methoxymethyl propyl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	408 46	1 56
398		5-(2 Ethyl 6 isopropo y pyr d 3 yl)-1 ((R)-1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin	396 51	1 54

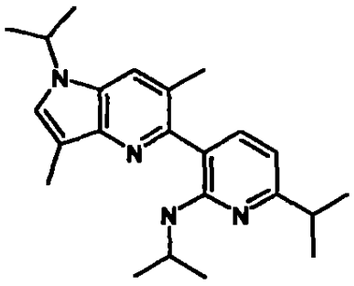
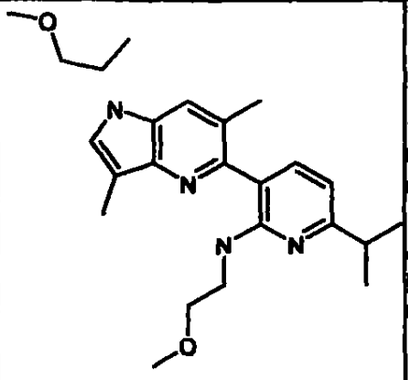
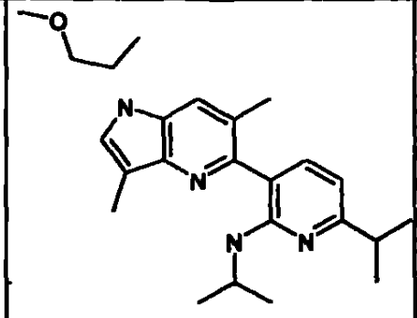
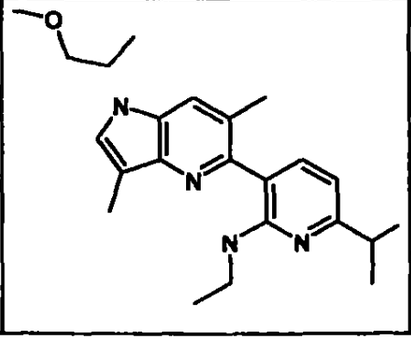
399		6 Ethyl 5-(2-ethyl 6 methoxy pyrid n 3 yl)-1-((R)-2 fluoro-1 methoxymethyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridine	386 44	1 44
400		5 [2 Ethyl 6-(2 methoxy ethoxy)-pyridin 3 yl] 1-((S) 2 methoxy 1 methyl ethyl)-3 6-dimethyl 1H-pyrrolo[3 2 b]py d e	398 34	1 41
401		5-(6-Isopropyl 2 methoxy py d n 3 yl)-1-((S)-2-methoxy 1 methyl-ethyl)-3 6 7 trimethyl 1H pyrrolo[3 2 b]pyr d	382 3	
402		{6-Isopropyl 3 [1 ((S)-2-methoxy 1-methyl ethyl)-3 6 7 tr methyl 1H pyrrolo[3 2 b]pyrid 5 yl] pyrid 2 yl}-methyl-am e	381 2	
403		5-(2 Ethyl-6 isopropyl pyrid n 3 yl) 1 ((S)-2 methoxy 1 methyl ethyl) 3 6 7 tr methyl 1H pyrrolo[3 2 b]pyrid ne	380 2	

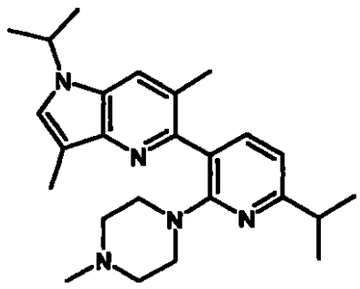
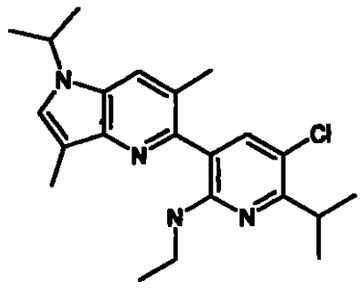
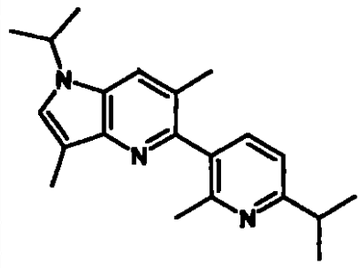
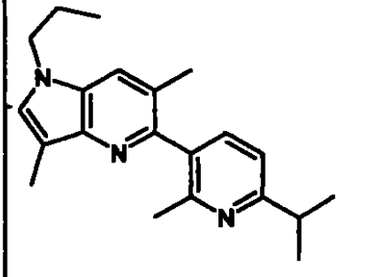
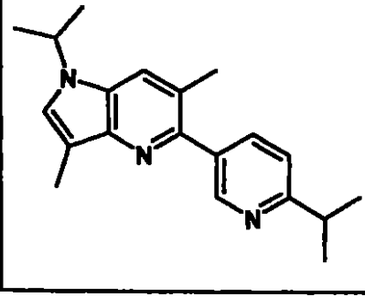
404		{6-Isopropyl-3-[1-((S)-2-methoxy-1-methyl-ethyl)-3,6,7-trimethyl-1H-pyrrolo[3,2-b]pyridin-5-yl]-pyridin-2-yl}-dimethyl-amine	395.3	
405		5-(2-Azetidin-1-yl-6-isopropyl-pyridin-3-yl)-1-((S)-2-methoxy-1-methyl-ethyl)-3,6,7-trimethyl-1H-pyrrolo[3,2-b]pyridine	407.6	
406		[3-(3,6-Dimethyl-1-propyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-6-isopropyl-pyridin-2-yl]-(2-methoxy-ethyl)-amine	381.3	1.95
407		6-Isopropyl-3-(1-isopropyl-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-pyridin-2-yl]-(2-methoxy-ethyl)-amine	381.3	1.88

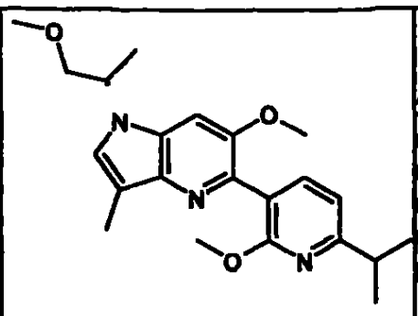
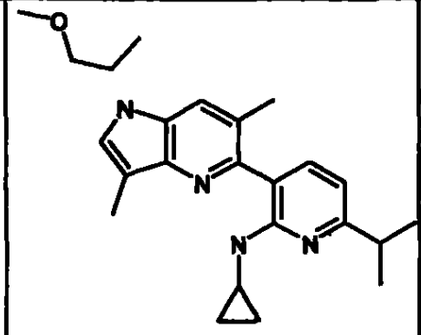
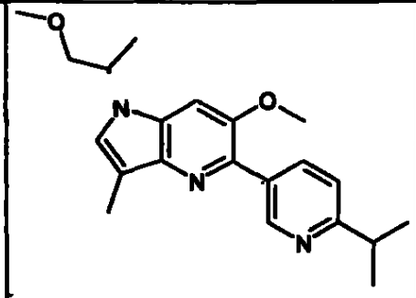
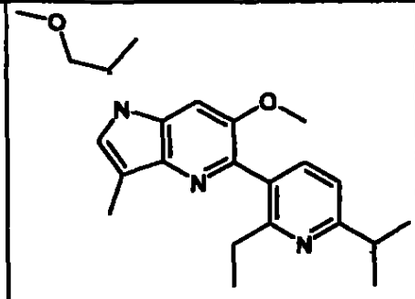
408		5-(6-Isopropyl 2 methoxy pyridin 3 yl)-1-((S)-2-methoxy 1 methyl-ethyl)-3 6 d methyl 1H pyrrolo[3,2 b]pyridin e	368 2	2 28
409		{6-Isopropyl 3 [1-((S)-2 methoxy 1 methyl ethyl) 3 6-dimethyl 1H pyrrolo[3 ,2 b]pyridi 5 yl]. pyridin-2 yl}-dimethyl am e	381 3	2 00
410		[6 Isopropyl 3-(1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyrid 5 yl)-pyrid 2 yl] d m thyl-amine	351 4	2 07
411		[3 (3 6 Dimethyl 1 propyl 1H-pyrrolo[3 2 b]pyridin-5 yl)-6 isopropyl pyrid n 2 yl] d methyl am ne	351 4	2 12

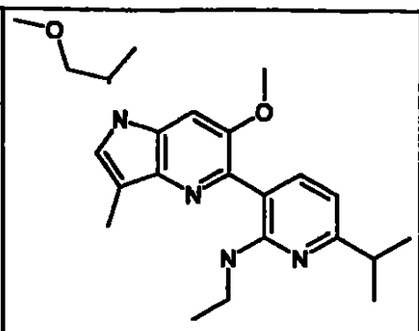
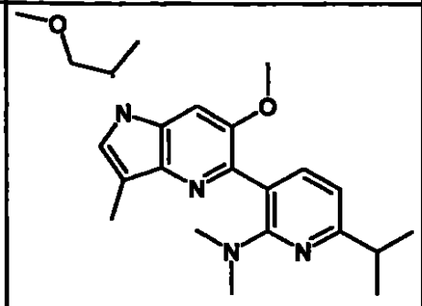
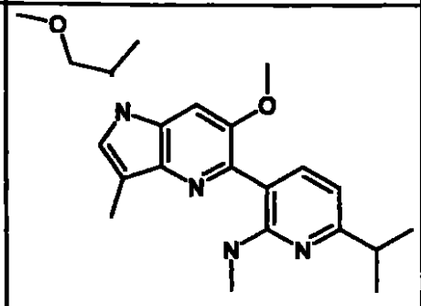
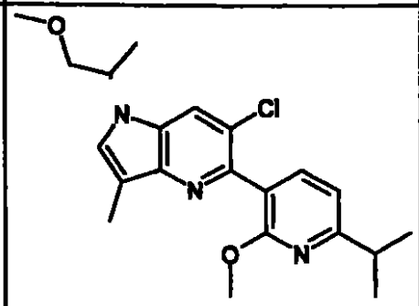
412		5-(2 Azetidin 1 yl-6-isopropyl-pyridin-3 yl) 3 6-dimethyl 1 propyl 1H pyrrolo[3,2 b]pyrid ne	363 4	1 87
413		5-(2 Azetidin 1 yl-6 isopropyl pyridin 3 yl)-1 sopropyl 3 6-d methyl 1H pyrrolo[3 2 b]pyr dine	363 4	1 87
414		5 (2 Azetid 1 yl-6-isopropyl py din 3 yl)-1-((S) 2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	393 4	1 75
415		5 [2-(3 3 D fluoro-azetidin 1 yl)-6-isopropyl pyridin-3 yl] 1-((S)-2 methoxy 1 methyl-ethyl) 3 6 d methyl 1H pyrrolo[3,2-b]pyr d	429.2	2 38

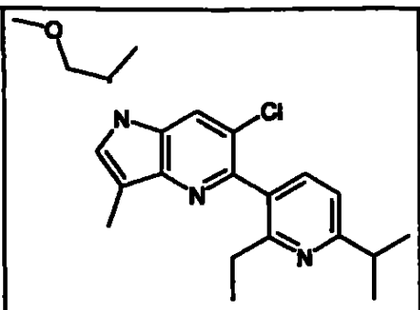
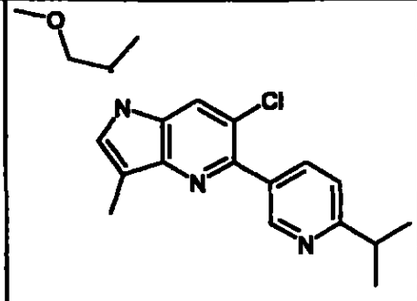
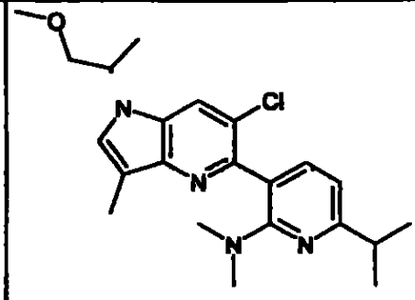
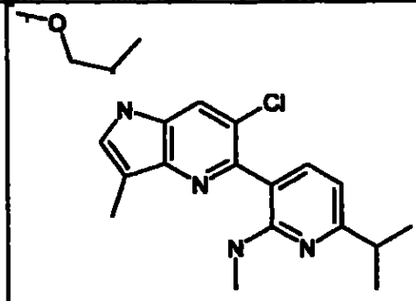
416		5 (2 Ethoxy-6-isopropyl pyridin 3 yl)-1-((S) 2 methoxy 1 methyl-ethyl)-3 6 d methyl 1H pyrrolo[3 2 b]pyridin	382 1	2 52
417		5-(2 Isopropoxy-6-isopropyl pyr d n 3 yl)-1-((S) 2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrol [3 2 b]pyridı	396 2	2 57
418		5-(6 Isopropyl 2 methyl pyridin 3 yl) 1 ((S)-2 methoxy 1 methyl-ethyl) 3 6-dimethyl 1H pyrrolo[3 2 b]pyridine	352 1	1 60
419		[3-(3 6 Dimethyl 1 propyl 1H pyrrolo[3 2 b]pyridin 5 yl)-6 isopropyl pyridin 2 yl] isopropyl mine	365 2	2 13

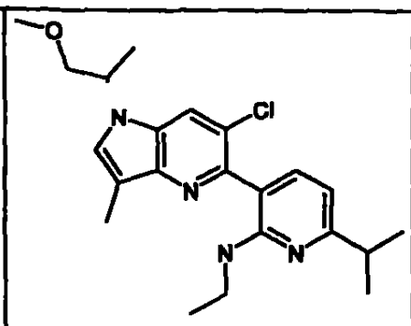
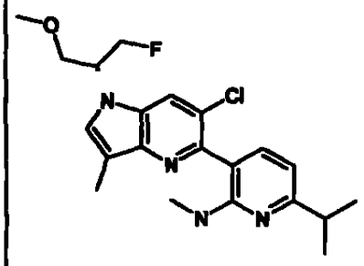
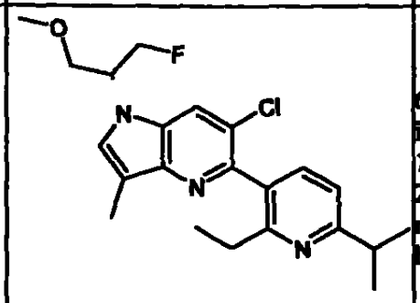
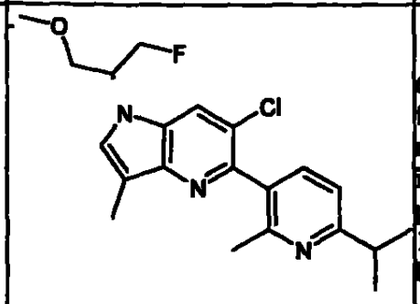
420		Isopropyl-[6-isopropyl 3-(1 sopropyl 3 6-dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl)-pyridin 2 yl] amine	365 2	2 1
421		{6-Isopropyl 3 [1-(2 methoxy 1 methyl ethyl) 3 6-dimethyl 1H pyrrolo[3 ,2-b]pyridin 5 yl] pyridin 2 yl} (2 methoxy-ethyl)-a	411.2	1 83
422		Isopropyl-{6-isopropyl 3 [1-((S) 2 methoxy 1 methyl-ethyl)-3 6-din ethyl 1H pyrrolo[3,2 b]py din 5 yl] pyridin 2 yl} amine	395 2	2 02
423		Ethyl {6- sopropyl 3 [1-((S)-2 methoxy 1 methyl-ethyl)-3 6 dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl] pyridin 2 yl} amine	381.2	1 77

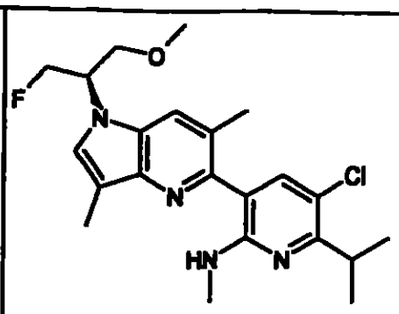
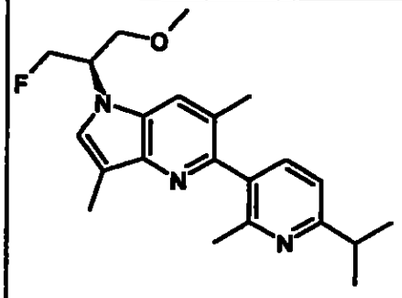
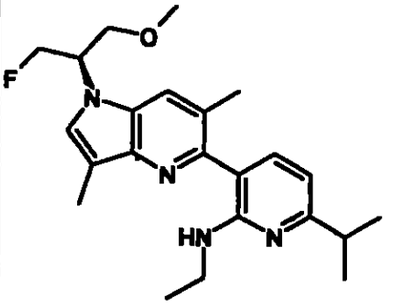
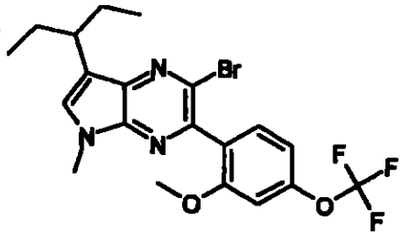
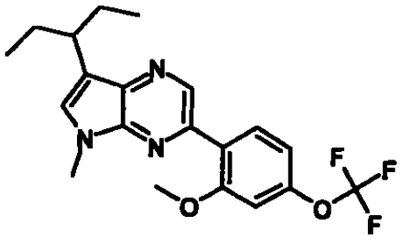
424		1 Isopropyl 5 [6-isopropyl 2-(4-methyl piperazin-1 yl)-pyridin 3 yl] 3 6-dimethyl-1H pyrrolo[3,2 b]pyridine	406 3	1 67
425		[5-Chloro-6-isopropyl 3-(1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyrid n 5 yl)-pyrid n 2 yl] ethyl-amine	385 2	2 78
426		1 Isopropyl 5-(6-isopropyl 2 methyl pyridin 3 yl)-3 6-d methyl 1H pyrrolo[3,2 b]pyridine	322 2	1 68
427		5-(6-Isopropyl 2 methyl pyridin 3 yl)-3 6-dimethyl 1 propyl 1H-pyrrolo[3,2 b]pyridine	322.2	1 72
428		1 Isopropyl 5-(6-isopropyl-pyrid n-3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine	308.2	1 85

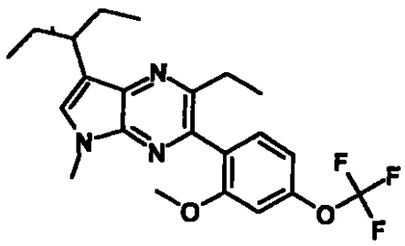
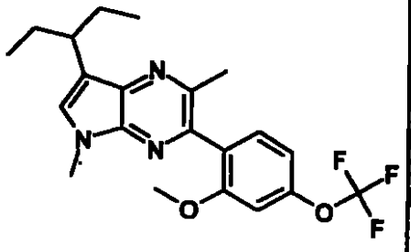
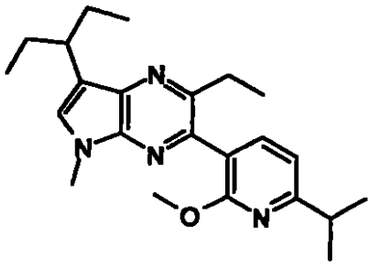
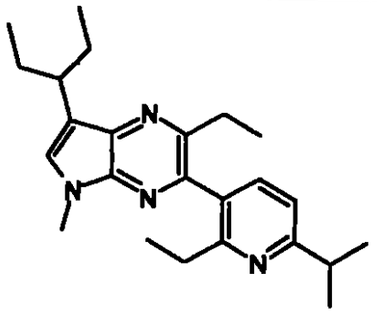
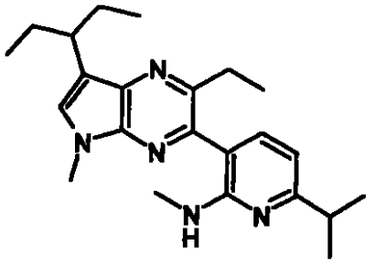
429		5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-6-methoxy 1-((S)-2 methoxy 1 methyl ethyl)-3-methyl-1H pyrrolo[3,2 b]pyridine	384.2	2 40
430		Cyclopropyl-{6-isopropyl 3 [1-((S)-2 methoxy-1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl] pyridin-2 yl}-amine	393 3	1 7
431		5-(6-Isopropyl-pyridin-3 yl)-6-methoxy 1-((S)-2 methoxy 1 methyl ethyl)-3-methyl 1H pyrrolo[3,2-b]pyridine	354.2	2 02
432		5-(2 Ethyl-6-isopropyl-pyridin 3 yl)-6-methoxy 1-((S)-2 methoxy-1 methyl ethyl)-3-methyl-1H pyrrolo[3,2 b]pyr idine	382.3	1 94

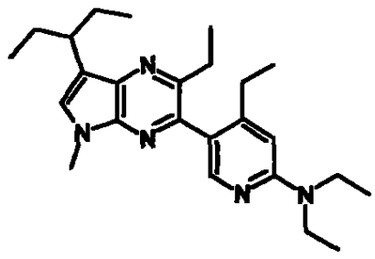
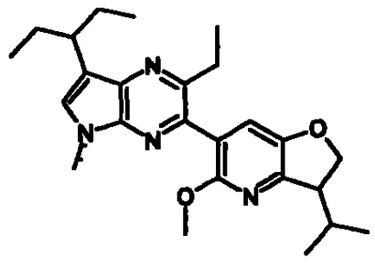
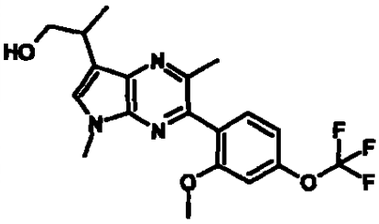
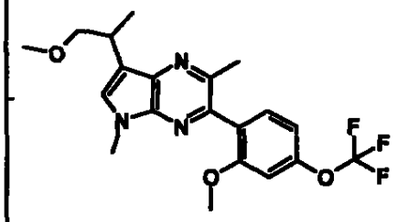
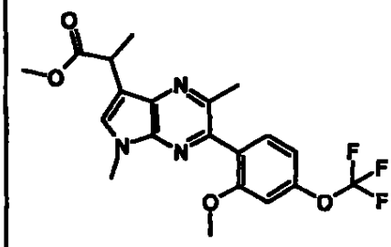
433		Ethyl {6-isopropyl-3 [6-methoxy 1-((S)-2 methoxy 1 methyl ethyl)-3-methyl-1H pyrrolo[3,2 b]pyridin 5 yl]-pyridin 2 yl} amine	397.3	2 14
434		{6-Isopropyl 3 [6-methoxy-1-((S) 2 methoxy 1-methyl ethyl)-3-methyl 1H pyrrolo[3,2 b]pyridin 5 yl] pyrid n 2 yl} dimethyl-amine	397 2	1 97
435		{6-Isopropyl 3 [6-methoxy 1-((S)-2 methoxy-1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl] pyridm 2 yl} methyl-amine	383.3	1 93
436		6-Chloro-5-(6-isopropyl 2 methoxy pyridm 3 yl)-1 ((S)-2 methoxy 1 methyl ethyl)-3 methyl 1H pyrrolo[3,2-b]pyridine	388 2	3 15

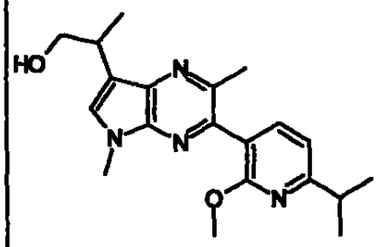
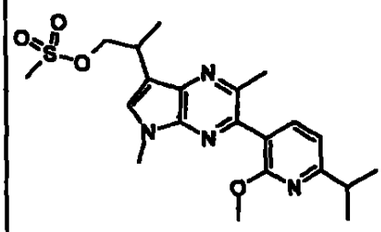
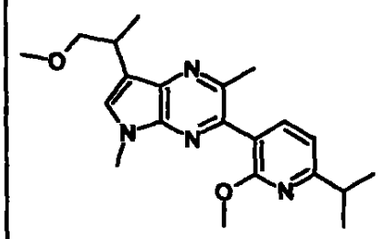
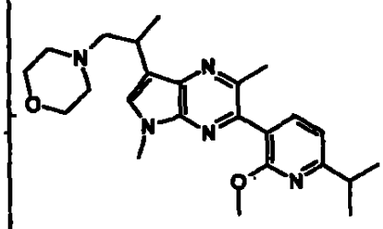
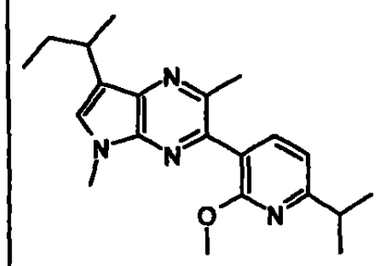
437		6-Chloro-5-(2-ethyl-6-isopropyl-pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl-1H pyrrolo[3,2 b]pyridine	386.2	2 02
438		6-Chloro-5-(6-isopropyl-pyridin 3 yl)-1-((S)-2-methoxy 1 methyl-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyridine	358.2	2 15
439		{3 [6-Chloro-1-((S)-2 methoxy-1 methyl-ethyl)-3-methyl 1H pyrrolo[3,2-b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-dimethyl amine	401.2	2 12
440		{3 [6-Chloro-1-((S)-2 methoxy 1-methyl ethyl)-3 methyl 1H pyrrolo[3 2-b]pyrid n 5 yl]-6-isopropyl pyridin 2 yl}-methyl-amine	387.2	2 09

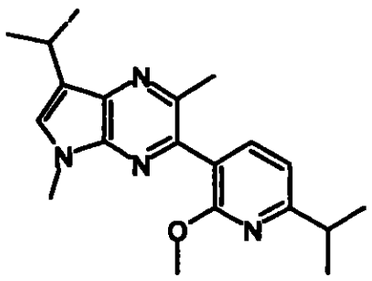
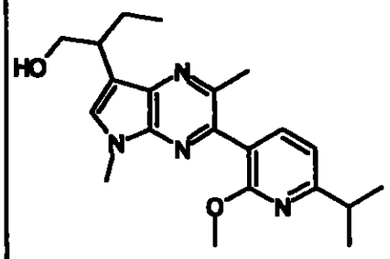
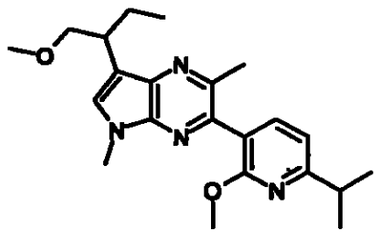
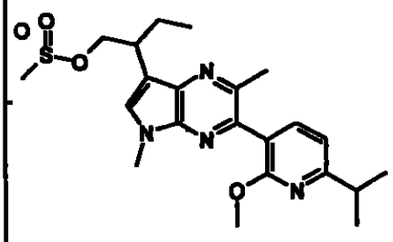
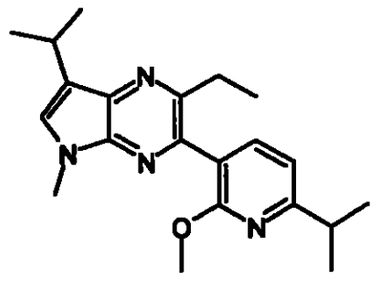
441		{3 [6-Chloro-1-((S)-2 methoxy-1 methyl ethyl)-3-methyl 1H pyrrolo[3,2-b]pyridin-5 yl]-6-isopropyl-pyridin 2 yl}-ethyl-amine	401.2	2.22
442		{3 [6-Chloro-1-((R)-1 fluoromethyl-2-methoxy-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridi 5 yl]-6-isopropyl pyridin-2 yl} methyl-amine	405 2	2 09
443		6-Chloro-5-(2-ethyl-6-isopropyl pyridin 3 yl)-1-((R)-1 fluoromethyl 2-methoxy-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridine	448 12	2 34
444		6-Chloro-1-((R)-1 fluoro-methyl 2 methoxy-ethyl)-5-(6-isopropyl 2 methyl pyridin-3 yl)-3-methyl 1H pyrrolo[3 2 b]pyridine	390 11	2 17

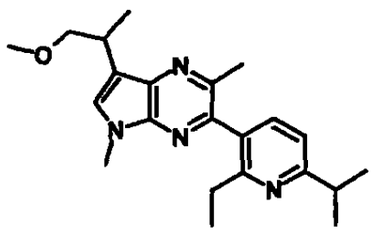
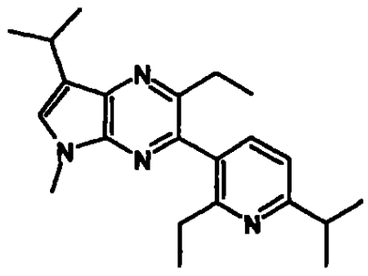
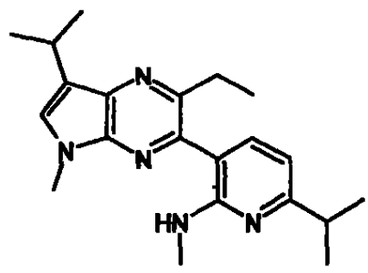
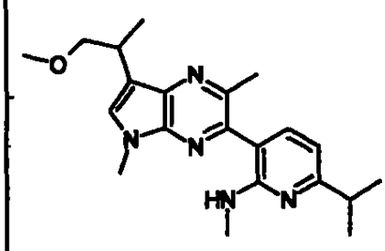
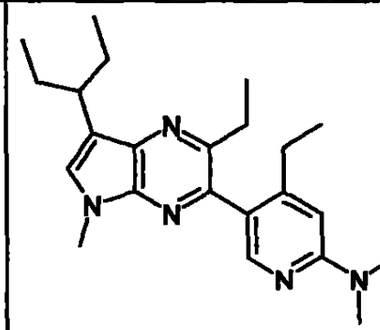
445		{5-Chloro-3 [1-((R)-1 fluoromethyl-2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl]-6-isopropyl pyridin 2 yl} methyl amine	419.2	2 67
446		1-(R)-1 Fluoromethyl-2 methoxy-ethyl)-5-(6-isopropyl 2-methyl pyridin-3 yl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridine	370.20	1 83
447		Ethyl {3 [1-((R)-1 fluoromethyl-2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-amine	399.20	2 03
448		2 Bromo-7-(1-ethyl propyl)-3-(2 methoxy-4-trifluoromethoxy phenyl)-5-methyl 5H pyrrolo[2,3-b]pyrazine	472.30	
449		7-(1 Ethyl-propyl)-3 (2-methoxy-4-trifluoromethoxy-phenyl)-5-methyl 5H pyrrolo[2 3-b]pyrazine	394.3	

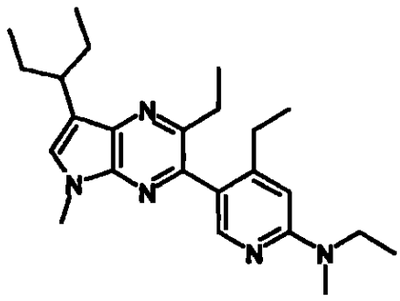
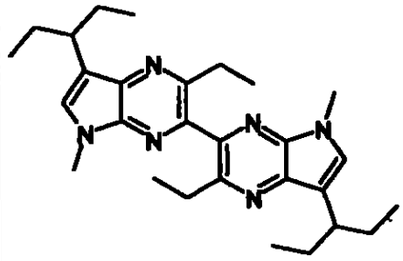
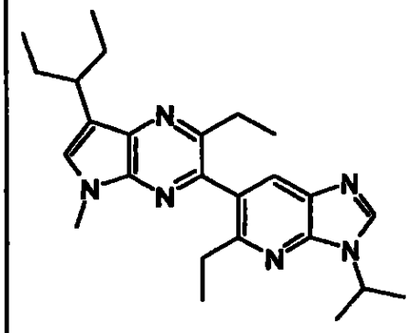
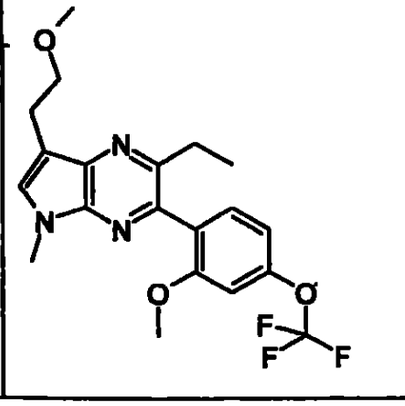
450		2 Ethyl 7-(1-ethyl propyl)-3-(2 methoxy 4-trifluoromethoxy-phenyl)-5-methyl 5H pyrrolo[2,3-b]pyrazine	422.5	
451		7-(1 Ethyl-propyl)-3 (2-methoxy-4 trifluoromethoxy-phenyl)-2 5-dimethyl 5H pyrrolo[2 3 b]pyrazine	408 5	
452		2 Ethyl 7-(1-ethyl propyl)-3-(6-isopropyl 2 methoxy pyrid n 3 yl)-5 methyl 5H pyrrolo[2 3-b]pyrazine	381 2	
453		2 Ethyl 3-(2-ethyl-6-isopropyl-pyridin 3 yl)-7 (1-ethyl-propyl)-5 methyl 5H-pyrrolo[2,3 b]pyrazine	379 4	
454		{3 [2 Ethyl 7-(1-ethyl propyl) 5 methyl 5H pyrrolo[2,3 b]pyrazin 3 yl]-6-isopropyl pyridin 2 yl} methyl amine	380 5	

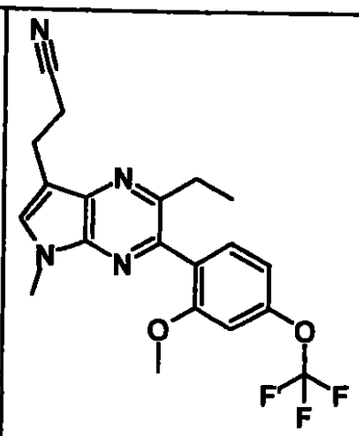
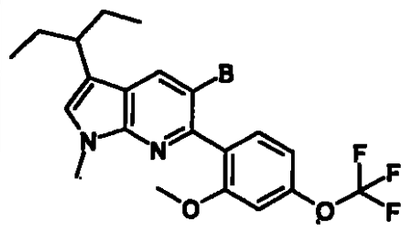
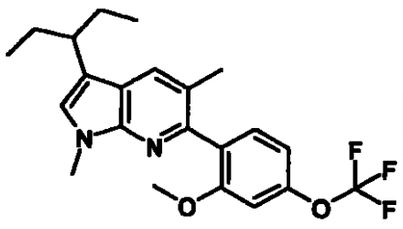
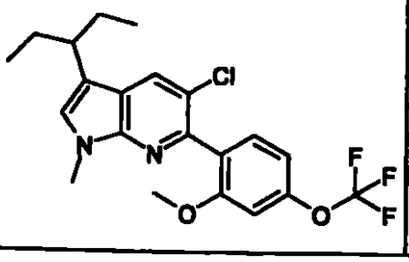
455		Diethyl-{4-ethyl 5-[2 ethyl 7-(1-ethyl-propyl)-5 methyl-5H pyrrolo[2,3 b]pyrazin-3 yl]-pyridin 2 yl} amine	408.37	1 54
456		2 Ethyl-7-(1-ethyl propyl)-3-(3-isopropyl 5 methoxy 2,3 dihydro-furo[3,2 b]pyridin-6-yl)-5 methyl 5H pyrrolo[2,3 b]pyrazine	423 14	1 92
457		2-[3-(2 Methoxy-4 trifluoromethoxy-phenyl)-2 5-dimethyl 5H-pyrrolo[2,3 b]pyrazin 7 yl] propan-1-ol	396 05	1 70
458		7-(2 Methoxy 1 methyl-ethyl)-3-(2 methoxy-4-trifluoromethoxy phenyl)-2 5-dimethyl 5H pyrrolo[2,3 b]pyrazine	410 03	1 77
459		2 [3-(2 Methoxy-4-trifluoromethoxy phenyl)-2,5-dimethyl 5H pyrrolo[2,3 b]pyrazin 7 yl] propionic acid methyl ester	424 00	1 74

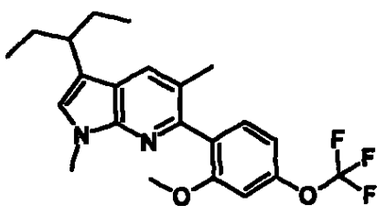
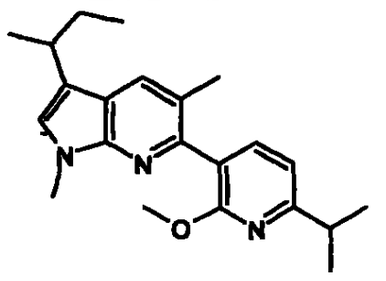
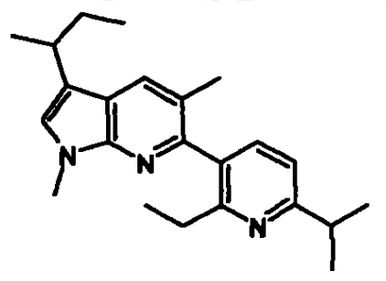
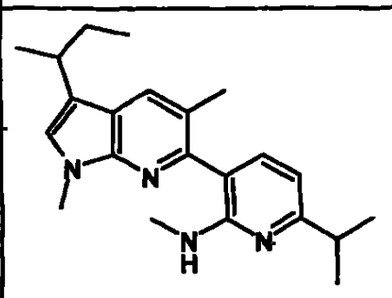
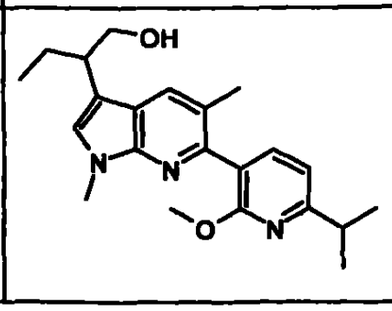
460		2 [3-(6-Isopropyl 2 methoxy pyridin 3 yl)-2,5-dimethyl 5H pyrrolo[2,3 b]pyrazin 7 yl] propan-1-ol	355 16	1 76
461		Methanesulfonic acid 2 [3-(6-isopropyl 2 methoxy-pyridin 3 yl)-2 5-dimethyl 5H pyrrolo[2 3 b]pyrazin 7 yl] propyl ester	433 07	1 77
462		3-(6-Isopropyl 2 methoxy pyr din 3 yl)-7-(2 methoxy 1 methyl-ethyl)-2 5 dimethyl 5H pyrrolo[2 3 b]pyrazine	369 15	1 83
463		3-(6-Isopropyl 2 methoxy pyridin-3 yl)-2,5-dimethyl 7-(1 methyl-2 morpholin-4 yl-ethyl)-5H pyrrolo[2 3 b]pyrazine	424 13	1 53
464		7-sec-Butyl 3-(6-isopropyl 2 methoxy pyridin-3 yl)-2 5 dimethyl 5H pyrrolo[2 3-b]pyrazine	353 18	1 89

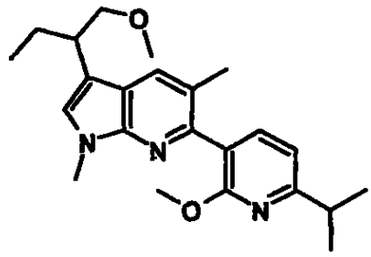
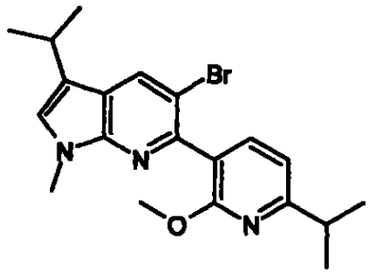
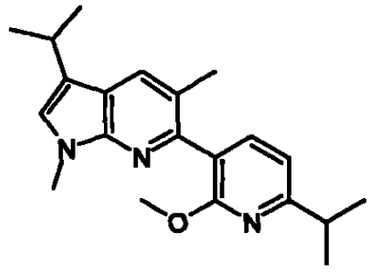
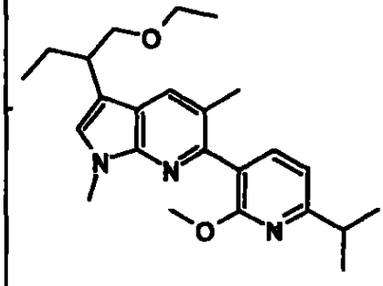
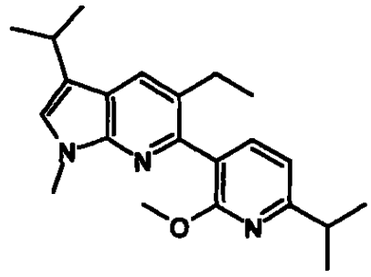
465		7 Isopropyl-3-(6-isopropyl 2-methoxy pyridin-3 yl)-2,5 dimethyl 5H pyrrolo[2 3 b]pyrazine	339 19	1 87
466		2 [3-(6-Isopropyl-2-methoxy-pyridin-3 yl)-2 5-dimethyl-5H pyrrolo[2 3 b]pyrazin-7 yl]-butan 1-ol	369 15	1 78
467		3-(6-Isopropyl 2 methoxy-pyridin 3 yl)-7-(1 methoxymethyl propyl)-2 5-dimethyl 5H pyrrolo[2 3 b]pyrazine	383 16	1 85
468		Methanesulfonic acid 2-[3-(6- sopropyl 2 methoxy-pyridin 3 yl)-2,5-dimethyl 5H pyrrolo[2 3 b]pyrazin 7 yl]-butyl ester	447 06	1 78
469		2 Ethyl 7 isopropyl 3 (6-isopropyl 2 methoxy-pyridin 3 yl)-5-methyl 5H pyrrolo[2 3-b]pyrazine	353 18	1 92

470		3-(2 Ethyl-6-isopropyl pyridin-3 yl)-7-(2 methoxy-1 methyl ethyl)-2 5-dimethyl-5H pyrrolo[2,3 b]pyrazine	367 18	1.36
471		2 Ethyl-3-(2-ethyl-6-isopropyl pyridin 3 yl)-7 isopropyl 5-methyl 5H pyrrolo[2,3 b]pyrazine	351 24	1 70
472		[3-(2 Ethyl 7 isopropyl 5 methyl 5H pyrrolo[2,3 b]pyrazin 3 yl)-6-isopropyl-pyrid n 2 yl] methyl amine	352 21	1 50
473		{6-Isopropyl 3-[7-(2 methoxy-1 methyl ethyl)-2,5-dimethyl 5H pyrrolo[2,3 b]pyrazin 3 yl] pyridin-2 yl}-methyl-amine	368 19	1 37
474		{4 Ethyl 5 [2-ethyl-7 (1-ethyl-propyl)-5 methyl 5H pyrrolo[2,3 b]pyrazin-3 yl] pyridin-2 yl}-dimethyl-amine	380 5	

475		Ethyl-{4-ethyl 5-[2 ethyl 7-(1-ethyl propyl)-5-methyl 5H pyrrolo[2,3-b]pyrazin-3-yl] pyridin-2 yl} methyl-amine	394.5	
476		2,2 Diethyl-7 7'-bis-(1 ethyl-propyl)-5 5 dimethyl 5H,5'H [3 3']bi[pyrrolo[2,3 b]pyrazinyl]	461.30	1 97
477		5 Ethyl-6-[2-ethyl 7-(1-ethyl propyl)-5-methyl 5H pyrrolo[2,3 b]pyrazin 3 yl]-3 isopropyl 3H imidazo[4 5 b]pyridine	419.38	1 78
478		2 Ethyl-7-(2 methoxy ethyl)-3-(2-methoxy-4-trifluoromethoxy phenyl)-5-methyl 5H pyrrolo[2,3 b]pyrazine	410 06	

479		3 [2 Ethyl 3-(2 methoxy-4-trifluoromethoxy phenyl)-5 methyl 5H pyrrolo[2,3-b]pyrazin 7 yl] propion trile	405 07	
480		5 Bromo-3-(1-ethyl propyl)-6-(2-methoxy 4-trifluoromethoxy phenyl)-1 methyl 1H pyrrolo[2 3 b]pyridine		
481		3-(1 Ethyl-propyl)-6-(2-methoxy-4 trifluoromethoxy-phenyl)-1 5-dimethyl 1H pyrrolo[2,3 b]pyridine	407 6	
482		5-Chloro-3-(1-ethyl propyl)-6-(2 methoxy 4-trifluoromethoxy phenyl)-1 methyl 1H pyrrolo[2,3-b]pyridi e		

483		3-(1 Ethyl-propyl)-6-(2-methoxy-4 trifluoromethoxy-phenyl)-1,5-dimethyl 1H pyrrolo[2,3 b]pyridine	407 6	
484		3-sec-Butyl-6-(6-isopropyl 2-methoxy pyridin-3 yl)-1,5 dimethyl-1H pyrrolo[2 3 b]pyridine	352 5	
485		3-sec-Butyl-6-(2-ethyl-6-isopropyl-pyridin 3 yl)-1 5-dimethyl 1H pyrrolo[2 3 b]pyridine	350 5	
486		[3-(3-sec-Butyl 1 5 dimethyl 1H pyrrolo[2,3-b]pyridin 6-yl)-6-isopropyl-pyridin-2 yl]-methyl-amine	351 4	
487		2 [6-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1 5-dimethyl 1H pyrrolo[2 3 b]pyridin-3 yl]-butan-1-ol	368 3	

488		6-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3-(1 methoxymethyl-propyl)-1,5-dimethyl 1H pyrrolo[2,3 b]pyridine	382.3	
489		5 Bromo-3 isopropyl 6-(6- sopropyl 2 methoxy pyridin 3 yl)-1-methyl 1H pyrrolo[2,3 b]pyridine	402 5	
490		3 Isopropyl 6-(6-isopropyl 2 methoxy pyridin 3 yl)-1 5 dimethyl 1H pyrrolo[2,3 b]pyridine	338 3	
491		3-(1 Ethoxymethyl propyl)-6-(6-isopropyl 2-methoxy-pyridin 3 yl)-1 5-dimethyl 1H pyrrolo[2 3 b]pyridine	396 5	
492		5 Ethyl 3 isopropyl 6-(6-isopropyl 2-methoxy pyridin 3 yl)-1 methyl 1H pyrrolo[2,3 b]pyridine	352 17	3 14

Example 51

Assay for CRF Receptor Binding Activity

As discussed above, the following assay is defined herein as a standard in vitro CRF receptor binding assay

The pharmaceutical utility of compounds of this invention is indicated by the following assay for CRF1 receptor activity The CRF-receptor binding is performed using a modified version of the assay described by Grigoriadis and De Souza (*Methods in Neurosciences* Vol 5 1991) IMR 32 human neuroblastoma cells, a cell-line that naturally expresses the CRF1 receptor are grown in IMR 32 Medium, which consists of EMEM w/Earle's BSS (JRH Biosciences, Cat# 51411) plus, as supplements, 2mM L-Glutamine, 10% Fetal Bovine Serum 25mM HEPES (pH 7.2), 1mM Sodium Pyruvate and Non Essential Amino Acids (JRH Biosciences, Cat# 58572) The cells are grown to confluence and split three times (all splits and harvest are carried out using NO-ZYME – JRH Biosciences, Cat# 59226) The cells are first split 1.2 incubated for 3 days and split 1 3 and finally incubated for 4 days and split 1 5 The cells are then incubated for an additional 4 days before being differentiated by treatment with 5 bromo-2 deoxyuridine (BrdU Sigma, Cat# B9285) The medium is replaced every 3-4 days with IMR 32 medium w/2 5uM BrdU and the cells are harvested after 10 days of BrdU treatment and washed with calcium and magnesium free PBS

To prepare receptor containing membranes cells are homogenized in wash buffer (50 mM Tris HCl, 10 mM $MgCl_2$, 2 mM EGTA, pH 7 4) and centrifuged at 48,000 x g for 10 minutes at 4°C The pellet is re-suspended in wash buffer and the homogenization and centrifugation steps are performed two additional times.

Membrane pellets (containing CRF receptors) are re-suspended in 50 mM Tris buffer pH 7 7 containing 10 mM $MgCl_2$ and 2 mM EDTA and centrifuged for 10 minutes at 48 000g Membranes are washed again and brought to a final concentration of 1500 ug/ml in binding buffer (Tris buffer above with 0 1 % BSA, 1 5 mM bacitracin and 0 01 mg/ml aprotinin) For the binding assay 100 ul of the membrane preparation are added to 96 well microtube plates containing 100 ul of ^{125}I-CRF (SA 2200 Ci/mmol, final concentration of 100 pM) and 50 ul of test compound Binding is carried out at room temperature for 2 hours Plates are then harvested on a BRANDEL 96 well cell harvester and filters are counted for gamma emissions on a Wallac 1205 BETAPLATE liquid scintillation counter Non specific binding is defined by 1 mM cold CRF IC_{50} values are calculated with the non-linear curve

fitting program RS/1 (BBN Software Products Corp Cambridge MA) The binding affinity for the compo nds of Formula I expressed as IC_{50} alue, generally ranges from about 0 5 nanomolar to about 10 micromolar Preferred compounds of Formula I exhibit IC_{50} values of less than or equal to 1.5 micromolar more preferred compounds of Formula I exhibit IC_{50} alues of less than 500 nanomolar still more preferred compounds of Formula I exhibit IC_{50} values of less than 100 nanomolar and most preferred compound of Formula I exhibit IC_{50} values of less than 10 nanomolar The compounds shown in Examples 1 33 have been tested in this assay and found to exhibit IC_{50} values of less than or equal to 4 micromolar

Example 52

Preparatio of radiolabeled probe compounds of the invention

The compounds of the inve tion are prepared as radiolabeled probes by carrying out their synthesis using precursors compris ng t least one atom that is a radioisotope Th radioisotope is preferably selected from of at least one of carbon (preferably ^{1} C) hydrogen (preferably ^{3}H), s lfu (preferably ^{35}S), or iod n (preferably ^{125}I) Such radiolabeled probes are conveniently synthesized by a radioisotope supplier speci lizing in custom synthes s of radiolabeled probe compo nds Such suppliers include Amersham Corporation Arlington Heights, IL Cambridge Isotope Laboratories, Inc Andover MA SRI International Menlo Park, CA Wizard Laboratories, West Sacramento, CA ChemSyn Laboratories, Lexena, KS American Radiolabeled Chemicals, Inc. St Louis, MO and Moravek Biochemicals Inc Brea, CA

Trit um labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acet c acid acid-catalyzed exchange in tritiated trifluoroacetic acid or heterogeneous-catalyzed exchange with tritium gas Such preparations are also conven ently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate In addition certain precursors may be subjected to tritium halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate

Example 53

Receptor autoradiography

Receptor autoradiography (receptor mapping) is carried out in vitro as described by Kuhar in sections 8 1 1 to 8 1 9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Examples

Example 54

Additional Aspects of Preferred Compounds of the Invention

The most preferred compounds of the invention are suitable for pharmaceutical use in treating human patients. Accordingly such preferred compounds are non-toxic They do not exhibit single or multiple dose acute or long term toxicity mutagenicity (e.g., as determined in a bacterial reverse mutation assay such as an Ames test) teratogenicity tumorogenicity or the like and rarely trigger adverse effects (side effects) when administered at therapeutically effective dosages

Preferably administration of such preferred compounds of the invention at certain doses (i e doses yielding therapeutically effective *in vivo* concentrations or preferably doses of 10 50 100 150 or 200 mg/kg administered parenterally or prefrerably orally) does not result in prolongation of heart QT intervals (i.e as determined by electrocardiography e g in guinea pigs, mini pigs or dogs) When administered daily for 5 or preferably ten days, such doses of such preferred compounds also do not cause liver enlargement resulting in an increase of liver to body weight ratio of more than 100%, preferably not more than 75% and more preferably not more than 50% over matched controls in laboratory rodents (e g. mice or rats) In another aspect such doses of such preferred compounds also preferably do not cause l ver enlargement resulting in an increase of liver to body weight ratio of more than 50%, preferably preferably not more than 25%, and more preferably not more than 10% over matched untreated controls in dogs or other non rodent mammals.

In yet another aspect such doses of such preferred compounds also preferably do not promote the release of liver enzymes (e g. ALT LDH or AST) from hepatocytes *in vivo* Preferably such doses do not elevate serum levels of such enzymes by more than 100%, preferably not by more than 75% and more preferably not by more than 50% over matched untreated controls in laboratory rodents Similarly concentrations (n culture media or other such solutions that are contacted and incubated with cells *n vitro*) equivalent to two, fold, preferably five-fold, and most preferably ten fold the minimum in vivo therapeutic

concentration do not cause release of any of such liver enzymes from hepatocytes into ulture medium *in v tro* above baseline levels seen in media from untreated cells.

Because side effects are often due to undesirable receptor activation or antagonism, preferred compounds of the invention exert their receptor-modulatory effects with high selectivity This means that they do not bind to certain other receptors (othe than CRF receptors) with high affinity but rather only bind to, acti ate, or inhibit the activity of such other receptors with affinity constants of greater than 100 nanomolar preferably greater than 1 micromolar more preferably greater than 10 micromolar and most preferably greater than 100 micromolar Such receptors preferably are selected from the group including ion channel receptors, including sodium ion channel receptors, neurotransmitter receptors such as alpha and beta-adrenergic receptors, muscarinic receptors (particularly m1 m2 and m3 receptors), dopamine receptors, and metabotropic glutamate receptors and also include histamine receptors and cytokine receptors, e g interleukin receptors, particularly IL-8 receptors. The group of other receptors to which preferred compounds do not bind with high affinity also I des GABA receptors, bioact ve pept d receptors (nclud ng NPY and VIP receptors), neurokinin receptors, bradykinin receptors (e g BK1 receptors and BK2 receptors) and hormone receptors (nclud ng thyrotropin releasing hormone receptors and melanocyte-concentrating hormone receptors)

Example 55

Absence of Sodium Ion Channel Activity

Preferred compou ds of the invention do not exhibit act ity as sod um ion channel blockers. Sodium channel acti ity may be measured a standard *in vitro* sodium channel binding assays such as the assay given by Brown et al (*J Neurosc* 1986, *265* 17995 18004) Preferred compounds of the in ention exh b t less than 15 percent inh bition and more preferably less than 10 percent inh bition of sodium channel specific ligand binding whe present at a concentration of 4 uM The sod um ion channel specific ligand used may be labeled batrachotoxinin tetrodotoxin or saxitoxin Such assays, including the assay of Brown referred to above are performed as a commercial service by CEREP Inc Redmond, WA

Alternatively sodi m ion channel activity may be measured *i vivo* n an assay of anti-epileptic act vity Anti-epileptic activ ty of compounds may be measured by the ab l ty of the compounds to inhibit hind limb extension in the supra maximal electro shock model

Male Han Wistar rats (150-200mg) are dosed i p with a suspension of 1 to 20 mg of test compound in 0.25% methylcellulose 2 hr prior to test. A visual observation is carried out just prior to testing for the presence of ataxia. Using auricular electrodes a current of 200 mA, duration 200 millisec, is applied and the presence or absence of hind limb extension is noted Preferred compounds of the invention do not exhibit significant anti-epileptic activity at the $p< 0.1$ level of significance or more preferably at the $p< 0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student s T test.

Example 56

Microsomal *in vitro* half-life

Compound half life values ($t_{1/2}$ values) may be determined via the following standard liver microsomal half life assay Pooled Human liver microsomes are obtained from XenoTech LLC, 3800 Cambridge St. Kansas s City Kansas, 66103 (catalog # H0610) Such liver microsomes may also be obtained from In Vitro Technologies, 1450 South Rolling Road Baltamore, MD 21227 or from Tissue Transformation Technologies, Edison Corporate Center 175 May Street, Suite 600 Edison, NJ 08837 Reactions are preformed as follows.

Reagents

Phosphate buffer 19 mL 0.1 M NaH_2PO_4, 81 mL 0.1 Na_2HPO adjusted to pH 7.4 with H_3PO_4

CoFactor Mixture 16.2 mg NADP 45.4 mg Glucose-6-phosphate in 4 mL 100 mM $MgCl_2$

Glucose-6-phosphate dehydrogenase 214.3 ul glucose-6-phosphate dehydrogenase suspension (Boehringer-Manheim catalog no 0737224 distributed by Roche Molecular Biochemicals, 9115 Hague Road P O Box 50414 Indianapolis IN 46250) is diluted into 1285.7 ul distilled water

Starting Reaction Mixture 3 mL CoFactor Mixture 1.2 mL Glucose-6-phosphate dehydrogenase

Reaction

6 test reactions are prepared, each containing 25 ul microsomes, 5 ul of a 100 uM solution of test compound and 399 ul 0.1 M phosphate buffer A seventh reaction is prepared as a

positive control conta ning 25 ul microsomes, 399 l 0 1 M phosphate buffer and 5 l of a 100 uM solution of a compound with known metabolic properties (e g DIAZEPAM o CLOZEPINE) Reactions are preincubated at 39 C for 10 minutes 71 ul Starting Reaction Mixture is added to 5 of the 6 test reactions and to the positive control, 71 ul 100 mM $MgCl_2$ is added to the sixth test reaction, which is used as a negative control At each time point (0 1 3 5 and 10 minutes) 75 ul of each reaction mix is pipetted into a well of a 96-well deep-well plate containing 75 ul ice-cold acetonitrile Samples are ortexed and centrifuged 10 minutes at 3500 rpm (Sorval T 6000D centrifuge, H1000B rotor) 75 ul of supernatant from each reaction is transferred to a well of a 96-well plate containing 150 ul of a 0 5 uM solution of a compound with a known LCMS profile (internal standard) per well LCMS analysis of each sample is carried out and the amount of unmetabolized test compound is measured as AUC compound concentration vs time is plotted, and the $t_{1/2}$ value of th test compound is extrapolated

Preferred compounds of the invention exhibit *in vitro* $t_{1/2}$ values of greater than 10 m utes and less than 4 ho rs. Most preferred compounds of the invention exhib t *vitro* $t_{1/2}$ alues of between 30 minutes and 1 hour in human liver microsomes

Example 57

MDCK Toxicity Assay

Compounds causing acute cytotoxicity will decrease ATP production by Madin Darby canine kidney (MDCK) cells in the following assay

MDCK cells, ATCC no CCL-34 (American Type Culture Collection, Manassas, VA) are maintained in sterile conditions following the instructions in the ATCC production information sheet. The PACKARD (Meriden, CT) ATP LITE-M Luminescent ATP detection kit, product no 6016941 allows measurement ATP production in MDCK cells

Prior to assay 1 ul of test compound or control sample is pipetted into PACKARD (Meriden, CT) clear bottom 96-well plates Test compounds and control samples are diluted in DMSO to give final concentration in the assay of 10 micromolar 100 micromolar or 200 micromolar Control samples are drug or other compounds having known toxicity properties

Confluent MDCK cells are trypsinized harvested and diluted to a concentration of 0 1 x 10^6 cells/ ml with warm (37°C) VITACELL Minimum Essential Medium Eagle (ATCC catalog # 30-2003) 100ul of cells n medium is pipetted into each of all but five wells of each 96-well plate Warm med m without cells (100ul) is pipetted n the remaining five

wells of each plate to provide standard curve control wells These w ils, to which no cells are added, are used to determine the standard curve The plates are then incubated at 37°C under 95% O_2, 5% CO_2 for 2 hours with constant shaking After incubation, 50 ul of mammalian cell lysis solution is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

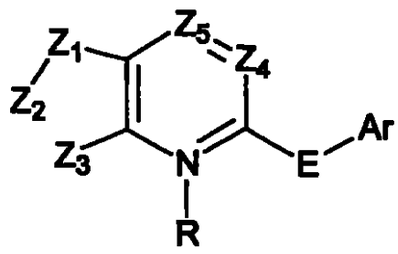
During the incubation, PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature Once equilibrated the lyophilized substrate solution is reconstituted in 5.5 mls of substrate buffer solution (from kit) Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 ul of serially diluted PACKARD standard is added to each of the five standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 M, 50 nM, 25 nM, and 12 5 nM

PACKARD substrate solution (50 ul) is added to all wells Wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 minutes. Luminescence is then measured at 22 C using a luminescence counter e g PACKARD TOPCOUNT Microplate Scintillation and Luminescense Counter or TECAN SPECTRAFLUOR PLUS.

Luminescence values at each drug concentration are compared to the values computed from the standard curve for that concentration Preferred test compounds exhibit luminescence values 80 % or more of the standard or preferably 90 % or more of the standard, when a 10 micromolar (uM) concentration of the test compound is used When a 100 uM concentration of the test compound is used, preferred test compounds exhibit luminescence values 50% or more of the standard or more preferably 80% or more of the standard

WHAT IS CLAIMED IS

1 A compound of the Formula I-a



Formula I-a

or a pharmaceutically acceptable salt thereof wherein

E is a single bond O $S(O)_m$, NR_{10} or $CR_{10}R_{11}$

R_{10} and R_{11} are independently hydrogen or C_1-C_4 alkyl

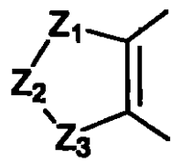
m is 0 1 or 2

Ar is chosen from

phenyl which is mono- di or tri-substituted 1 naphthyl and 2-naphthyl each of which is optionally mono- di or tri-substituted, and optionally mono- di or tri-substituted heteroaryl said heteroaryl ha g from 1 to 3 r gs, 5 to 7 r g members each ring nd in at least one of sa d r ngs, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

R is oxygen or absent,

the group



represents a saturated, nsaturated or aromatic 5-membered ring system containing 0 or 1 heteroatoms, where n

Z is CR or CR_1R_1

Z_2 is nitrogen, oxygen sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen, oxygen sulfur sulfoxide sulfone, CR_3, or CR_3R_3

R is chosen from hydrogen halogen hydroxy cyano amino, opt onally substituted alkyl optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy optionally substituted mono or dialkylamino, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl optionally substituted alkylthio, optionally substr ted alkylsulf nyl optionally subst tuted alkylsulfonyl optionally

substituted mono- or dialkylcarboxamide, optionally substituted carbocyclic aryl, optionally substituted heterocycle and optionally substituted heteroaryl, said optionally substituted heterocycle or heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

R_2 and R_3 are independently chosen from hydrogen, halogen, hydroxy amino, cyano, nitro, alkyl, haloalkyl, alkoxy aminoalkyl, hydroxyalkyl and mono and dialkylamino, wherein when R_1 or R_4 is optionally substituted alkyl, then R_3 is optionally substituted C_{1-3}alkyl

R_1 R_2 and R_3 are independently chosen from hydrogen halogen, alkyl haloalkyl, and aminoalkyl

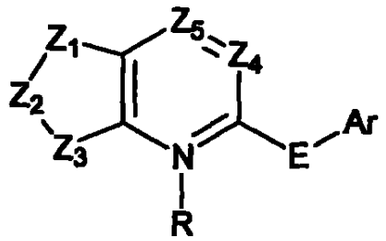
R_2 is chosen from hydrogen, optionally substituted alkyl optionally substituted haloalkyl, and opt onally substituted aminoalkyl

Z_4 is NR or CR_4

Z_5 is NR or CR_5

R_4 and R_5 are independently chosen from hydrogen, halogen, hydroxy amino, cyano n tro, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy optionally substituted mono or dialkylamino, optionally substituted (cycloalkyl)alkyl, optionally substituted alkylthio, optionally substituted alkylsulfinyl optionally substituted alkylsulfonyl optionally substituted mono- or dialkylcarboxamide optionally substituted carbocyclic aryl and optionally substituted heteroaryl said optionally substituted heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

2 A compound of the Formula I-a



Formula I-a

or a pharmaceutically acceptable salt thereof, wherein

E is a single bond, O $S(O)_m$, NR or $CR_{10}R_{11}$

R_{10} and R_{11} are independently hydrogen or C_1-C_4 alkyl

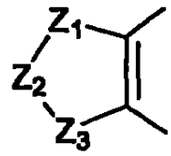
m is 0 1 or 2

R is oxygen or absent,

Ar is chosen from

phenyl which is mono- di or tri-substituted with R_A and 1 naphthyl 2-naphthyl, pyridyl, pyrimidinyl, pyrazinyl, pyridiz nyl thienyl th azolyl oxazolyl isoxazolyl pyrrolyl, furanyl and triazolyl each of which is optionally mono- di or tri-substituted with R_A

the group



represents a saturated, unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z is CR or CR R_1

Z_2 is nitrogen, oxygen, sulfu CR_2 CR_2R_2 or NR_2

Z_3 is nitrogen oxygen, sulfu sulfoxide sulfone CR_3 or CR_3R_3

R_1 is chosen from

i) hydrogen halogen hydroxy yano, amino, C_1-C_6alkyl -O(C_1-C_6 alkyl) mono or di(C_1 C_6alkyl)amino, (C_3-C_7cycloalkyl)C_1-C_4alkyl, halo(C_1-C_6)alkyl -O(halo(C_1-C_6)alkyl) and $S(O)_m$(C -C_6alkyl) -O(C_3-C_7cycloalkyl)C -C_4alkyl and $S(O)_m$(C_1-C_6alkyl)

where each alkyl is independently straight, branched or cyclic, conta ns zero or 1 or more double or triple bonds, and is optionally substituted with one or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C C_1 C_4alkoxy and mono- or di(C -C_4)alkylamino

and

where each C_3-C_7cycloalkyl is optionally substituted by one or more substituents independently chosen from halogen, am no, hydroxy oxo cyano, C_1-C_4alkoxy and mono- or di(C -C_4)alkylamino, and

ii) phenyl which is mono- di or tri-substituted with R_A 1 naphthyl, 2-naphthyl pyridyl, dihydropyridyl tetrahydropyridyl pyrimidinyl pyrazinyl pyridizinyl thienyl thiazolyl, oxazolyl isoxazolyl pyrrolyl furanyl and triazolyl, each of which is optionally mono- di o tri-substituted with R_A

R_2 and R_3 are independently chosen from hydrogen, halogen, hydroxy amino cyano, nitro, C_1-C_3alkyl halo(C_1-C_3)alkyl, C_1-C_3alkoxy amino(C_1-C_3)alkyl and mono and di(C_1-C_6)alkylamino

R_1 R_2 and R_3 are independently chosen from hydrogen, halogen, C_1-C_6alkyl halo(C_1-C_6)alkyl and amino(C_1-C_6)alkyl

R_2 is chosen from hydrogen, C_1-C_6alkyl halo(C_1-C_6)alkyl, and amino(C_1-C_6)alkyl

Z_4 is NR or CR_4

Z_5 is NR or CR_5

wherein Z_4 and Z_5 are not both NR,

R_4 and R_5 are independently chosen from hydrogen halogen, cyano, nitro, amino mono or di(C_1-C_6carbhydryl)amino, C_1-C_6carbhydryl, (C_3-C_7cyclocarbhydryl)C_0-C_6carbhydryl -O(C_3-C_7cyclocarbhydryl) halo(C_1-C_6)carbhydryl, -O(halo(C_1-C_6)carbhydryl) -O(C_1-C_6carbhydryl), and S(O)$_n$(C_1-C_6carbhydryl),

where each carbhydryl is independently straight, branched, or cycl contains zero or 1 or more double or triple bonds, and is optionally substituted with one or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano C_1-C_4alkoxy and mono- and di(C_1-C_4)alkylamino

and

where each C_1-C_7carbhydryl is optionally substituted by one or more substituents independently chosen from halogen, amino, hydroxy oxo cyano C_1-C_4alkoxy and mono- and di(C_1-C_4)alkylamino

R_A is independently selected at each occurrence from halogen, cyano, nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino C_1-C_6alkyl substituted with 0-2 R_B, C_2-C_6alkenyl substituted with 0-2 R_B, C_2-C_6alkynyl substituted with 0-2 R_B, C_3-C_7cycloalkyl substituted with 0-2 R_B (C_3-C_7cycloalkyl) C_1-C_4alkyl substituted w th 0 2 R_B, C_1-C_6alkoxy substituted with 0-2 R_B, NH(C_1-C_6alkyl) substituted with 0-2 R_B, N(C_1-C_6alkyl)(C_1-C_6alkyl) each C_1-C_6alkyl independently substituted with 0-2 R_B XR_C and Y

R_B is independently selected at each occurrence from the group consisting of halogen, hydroxy cyano amino C_1-C_4alkyl -O(C_1-C_4alkyl) NH(C_1-C_4alkyl) N(C_1-C_4alkyl)(C_1-C_4alkyl), S(O)$_n$(alkyl), halo(C_1-C_4)alkyl, halo(C_1-C_4)alkoxy CO(C_1-C_4alkyl), CONH(C_1-C_4alkyl), CON(C_1-C_4alkyl)(C_1-C_4alkyl) XR_C and Y

R_C and R_D, which may be the same or different, are independently selected at each occurrence from

hydrogen and straight, branched, or cyclic alkyl groups, including (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, which straight, branched or cyclic alkyl groups contain zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy halogen, cyano, amino C_1-C_6alkoxy $NH(C_1$-C_6alkyl) $N(C_1$-C_6alkyl)$(C_1$-C_6alkyl) $NHC(=O)(C_1$-C_6alkyl), $N(C_1$-C_6alkyl)$C(=O)(C_1$-C_6alkyl) $NHS(O)_n(C_1$-C_6alkyl), $-S(O)(C_1$-C_6alkyl), $S(O)_nNH(C_1$-C_6alkyl), $S(O)_nN(C_1$-C_6alkyl$)(C_1$-C_6alkyl) and Z,

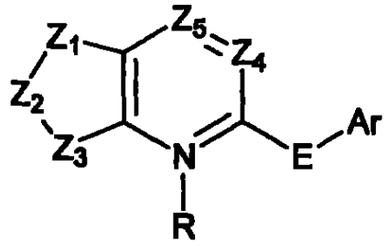
X is independently selected at each occurrence from the group consisting of $-CH_2-$ $-CHR_D-$ O- -C(=O)- -C(=O)O- $S(O)_n$ NH NR_D- -C(=O)NH -C(=O)NR_D- $-S(O)_nNH$ $-S(O)_nNR_D$- -OC(=S)S NHC(=O)- $NR_DC(=O)$- $NHS(O)_n$ $-OSiH_2-$ $-OSiH(C_1$-C_4alkyl)- $-OSi(C_1$-C_4alkyl$)(C_1$-C_4alkyl)- and $-NR_DS(O)_n$

Y and Z are independently selected at each occurrence from 3 to 7-membered carbocyclic or heterocyclic groups which are saturated unsaturated, or aromatic, which may be further substituted with one or more substituents independently selected from halogen, oxo, hydroxy amino cyano, C_1-C_4alkyl -O(C_1-C_4alkyl) $NH(C_1$-C_4alkyl), $N(C_1$-C_4alkyl$)(C_1$-C_4alkyl) and $-S(O)_n$(alkyl),

where n said 3 to 7 memberered heterocyclic groups contain one or more heteroatom(s) ndependently selected from N O and S with the point of attachment being either carbon or nitrogen and

n is independently selected at each occurrence from 0 1 and 2

3 A compound of the Formula I b



Form Ia I b

or a pharmaceutically acceptable salt thereof wherein

E is a single bond O $S(O)_m$, NR_{10} or $CR_{10}R_{11}$

R_0 and R_1 are independently hydrogen or C_1-C_4 alkyl

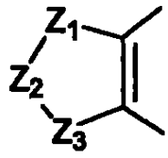
m is 0 1 or 2

R is oxygen or absent;

Ar is chosen from

phenyl which is mono- di or tri-substituted, 1 naphthyl and 2 naphthyl, each of which is optionally mono- di or tri-substituted, and optionally mono- di or tri-substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

the group



represents a saturated, unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z_1 is CR_1 CR R_1 or NR_1

Z_2 is CR_2 or CR_2R_2

Z_3 is CR_3 CR_3R_3 or NR_3

R_1 and R_1 are chosen from hydrogen, C_1-C_{10}alkyl, C_2-C_{10}alkenyl C_2-C_{10}alkynyl, C_3-C_7cycloalkyl, (benzo)C_3-C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl C_3-$_9$heterocycloalkyl, (C_{3-9}heterocycloalkyl)C_1-C_4alkyl, (benzo)C_{3-9}heterocycloalkyl, ((benzo)C_{3-9}heterocycloalkyl)C_1-C_4alkyl and halo(C -C_6)alkyl each of which is substituted with 0 or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C_1-C_6alkyl, C_1-C_6alkoxy haloC_1-C_6alkoxy C_1-C_6alkanoyl, C_1-C_6alkanoyloxy C_1-C_6alkoxycarbonyl,, N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, C -C_6alkylsulfonamide, C_1-C_6alkylsulfonyl C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C -C_6alkoxyC_1-C_6alkyl C -C_6haloalkoxy 5 to 7 membered heteroaryl 5 to 7 membered heterocycloalkyl mono- and di-(C_1-C_6)alkylamino, N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, mono- and di-(C_1-C_6)alkylcarbamoyl XR_C and X Z, with the proviso that R and R is not aryl or heteroaryl substituted alkyl

R_2 is chosen from hydrogen, halogen, hydroxy amino, cyano, nitro, C -C_3alkyl, halo(C_1-C_3)alkyl C_1-C_3alkoxy amino(C_1-C_3)alkyl and mono and di(C_1-C_6)alkylamino

R_3 is chosen from hydrogen hydroxy amino, halogen cyano, nitro, C_1-C_3alkyl, halo(C_1-C_3)alkyl, C_1-C_3alkoxy amino(C_1-C_3)alkyl hydroxy(C_1-C_3)alkyl cyano(C_1-C_3)alkyl and mono and di(C_1-C_3)alkylamino

R_3 is chosen from hydrogen hydroxy amino, C_1-C_3alkyl halo(C_1-C_3)alkyl C -C_3alkoxy amino(C_1-C_3)alkyl hydroxy(C_1-C_3)alkyl cyano(C -C_3)alkyl and mono and di(C_1-C_3)alkylamino

R_1 R_2 and R_3 are independently chosen from hydrogen halogen C_1-C_6alkyl halo(C-C_6)alkyl, and amino(C_1-C_6)alkyl,

Z_4 is NR or CR_4

Z_5 is NR or CR_5,

R_4 and R_5 are independently chosen from hydrogen halogen, cyano nitro amino mono or di(C_1-C_6carbhydryl)amino, C_1-C_6carbhydryl (C_3-C_7cyclocarbhydryl)C_0-C_6carbhydryl, -O(C_3-C_7cyclocarbhydryl), halo(C -C_6)carbhydryl, -O(halo(C-C_6)carbhydryl), -O(C_1-C_6carbhydryl), S(O)$_n$(C -C_6carbhydryl) nd 4 to 7 membered heterocycloalkyl

where each carbhydryl is independently straight, branched, or cyclic, contains zero or 1 or more double or triple bonds and is optionally substituted with one or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C_1-C_4alkoxy and mono- and di(C_1-C_4)alkylamino,

and

where each C_3-C_7carbhydryl heterocycloalkyl is optionally substituted by one or more substituents independently chosen from halogen, amino, hydroxy oxo, cyano, C_1-C_4alkoxy nd mono- and di(C_1-C_4)alkylamino or

R_5, taken in combination with R or R_1 forms a 5-9 membered heterocycle

R_A is independently selected at each occurrence from halogen cyano nitro halo(C_1-C_6)alkyl halo(C_1-C_6)alkoxy hydroxy amino C_1-C_6alkyl substituted with 0-2 R_B, C_2-C_6alkenyl substituted with 0 2 R_B, C_2-C_6alkynyl substituted with 0-2 R_B, C_3-C_7cycloalkyl s bstituted with 0-2 R_B, (C_3-C_7cycloalkyl)C_1-C_4alkyl substituted with 0-2 R_B, C_1-C_6alkoxy substituted with 0-2 R_B, NH(C -C_6alkyl) substituted with 0-2 R_B, N(C_1-C_6alkyl)(C_1-C_6alkyl) each C_1-C_6alkyl independently substituted with 0-2 R_B XR_C and Y

R_B is independently selected at each occurrence from the group consisting of halogen, hydroxy cyano amino, C_1-C_4alkyl, -O(C_1-C_4alkyl), NH(C_1-C_4alkyl), N(C_1 C_4alkyl)(C -C_4alkyl), S(O)$_n$(alkyl), halo(C_1-C_4)alkyl halo(C_1-C_4)alkoxy CO(C_1 C_4alkyl), CONH(C_1-C_4alkyl) CON(C_1-C_4alkyl)(C_1-C_4alkyl), XR_C and Y

R_C and R_D, which may be the same or different, are independently selected at each occurrence from

hydrogen, and

straight, branched, or cyclic alkyl groups, including (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, which straight, branched, or cyclic alkyl groups contain zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy halogen, cyano, amino, C_1-C_6alkoxy NH(C_1-C_6alkyl) N(C_1 C_6alkyl)(C_1-C_6alkyl), NHC(=O)(C_1-C_6alkyl), N(C_1-C_6alkyl)C(=O)(C_1-C_6alkyl), NHS(O)$_n$(C_1-C_6alkyl), -S(O)$_n$(C_1-C_6alkyl), S(O)$_n$NH(C_1-C_6alkyl), -S(O)$_n$N(C_1 C_6alkyl)(C_1-C_6alkyl), and Z

X is ind pendently selected at each occurrence from the group consisting of -O- -C(=O)O- S(O)$_n$ NH NR_D- -C(=O)NH -C(=O)NR_D- -S(O)$_n$NH S(O)$_n$$NR_D$- -OC(=S)S- NHC(=O)- NR_DC(=O)- NHS(O)$_n$ -OSiH$_2$ -OSiH(C_1-C_4alkyl)- -OSi(C_1-C_4alkyl)(C_1-C_4alkyl)- and -NR_DS(O)$_n$

Y and Z are independently selected at each occurrence from 3 to 7-membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic which may be further substituted w th one or more substituents independently selected from halogen, oxo hydroxy amino, cyano, C_1-C_4alkyl -O(C_1-C_4alkyl) NH(C_1-C_4alkyl), N(C_1-C_4alkyl)(C_1-C_4alkyl) -C(O)(C_1-C_4alkyl) and S(O)$_n$(alkyl) wherein said 3 to 7-memberered heterocyclic groups contain one or more heteroatom(s) independently selected from N O and S, with the point of attachment being either carbon or nitrogen and

n is independently selected at each occurrence from 0 1 and 2

4 A compound or salt according to laim 3 wherein

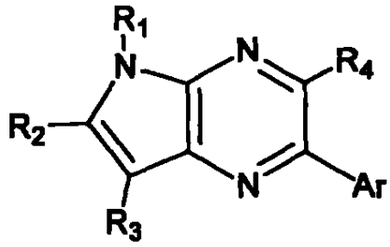
Ar is chosen from

phenyl which is mono- di or tri-substituted with R_A, and 1 naphthyl 2 naphthyl, pyridyl pyrimidinyl pyrazinyl pyridizinyl thienyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolyl,

furanyl and triazolyl each of which is optionally mono- di or tri-substituted with R_A and

R_1 and R_1 are chosen from hydrogen C_1-C_{10}alkyl C_2-C_{10}alkenyl C_2-C_{10}alkynyl C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C -C_4alkyl C_3-$_9$heterocycloalkyl (C_3-$_9$heterocycloalkyl)C_1-C_4alkyl and halo(C_1-C_6)alkyl each of which is substituted with 0 1 2, or 3 substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C -C_6alkyl C_1-C_6alkoxy haloC$_1$-C_6alkoxy C_1-C_6alkanoyl C_1-C_6alkanoyloxy C -C_6alkoxycarbonyl N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N (C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)am no N-(C -C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, C_1 C_6alkylsulfonamide, C_1-C_6alkylsulfonyl C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C_1-C_6alkoxyC -C_6alkyl, C_1-C_6haloalkoxy 5 to 7 membered heteroaryl, 5 to 7 membered heterocycloalkyl mono- and di-(C_1-C_6)alkylamino N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino mono- and di-(C_1-C_6)alkylcarbamoyl XR_C d X Z.

5 A compound or salt accord ng to Claim 3 of Formula II



Formula II

wherein R_1 R_2, R_3, R_4 and Ar are as defined in Cla m 3

6 A compound or salt according to Claim 5 wherein

R_1 is as defined for Cla m 3

R_2 is selected from hydrogen methyl and ethyl

R_3 s hydrogen or C_1-C_3alkyl

R_4 is selected from hydrogen halogen cyano, amino C -C_6alkyl C -C_6alkoxy C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C_1-C_4alkyl (C_3-C_7cycloalkyl)C -C_6alkoxy mono and di(C_1-C_6alkyl)amino, amino(C_1-C_6)alkyl mono and di(C_1-C_6alkyl)amino(C_1-C_6)alkyl halo(C_1-C_6)alkyl and halo(C_1-C_6)alkoxy and

cyano, C_1-C_6alkyl C_1-C_6alkoxy C -C_6hydroxyalkyl, C -C_6alkoxyC_1-C_6alkyl, (C_1 C_6)haloalkyl, (C_1-C_6)haloalkoxy mono- and di-(C_1-C_6)alkylamino, XR_C

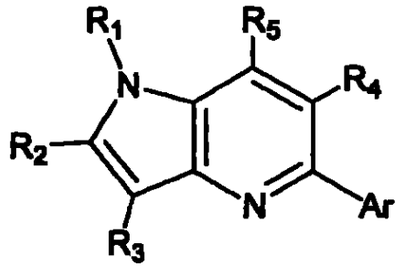
14 A compound or salt according to Claim 13 wherein

R_1 is chosen from tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl [2.2 1]-azabicyclic rings, [2.2.2]-azabicyclic rings, [3 3 1]-azabicyclic rings, quinuclidinyl, azetidinyl azetidinonyl, oxindolyl, dihydroimidazolyl, and pyrrolidinonyl, each of which is substituted with from 0 to 2 substituents independently chosen from

(i) halogen, hydroxy amino cyano, or

(ii) C_1-C_4alkyl, C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino, each of which is substituted with 0 or 1 substituents selected from halogen, hydroxy amino, C_{1-2}alkoxy or C_{3-5}heterocycloalkyl

15 A compound or salt according to Claim 3 of Formula VIII



Formula VIII

wherein R_1 R_2, R_3, R_4, R_5, and Ar are as defined in Claim 3

16 A compound or salt according to Claim 15 wherein

R_1 is as defined for Claim 3

R_2 is selected from hydrogen, methyl and ethyl

R_3 is C_1-C_3alkyl

R_4 and R_5 are independently selected from hydrogen, halogen, cyano amino, C -C_6alkyl C_1 C_6alkoxy C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C_1-C_4alkyl (C_3-C_7cycloalkyl)C C_4alkoxy mono and di(C_1-C_6alkyl)amino, amino(C_1-C_4)alkyl mono and di(C_1 C_6alkyl)amino(C_1-C_6)alkyl halo(C_1-C_6)alkyl, and halo(C_1-C_6)alkoxy and

Ar is selected from the gro p consisting of phenyl pyridyl and pyrimidinyl each of which is mono- di or trisubstituted with substituents independently chosen from halogen

cyano, nitro, halo(C_1-C_6)alkyl halo(C_1-C_6)alkoxy hydroxy amino C -C_6alkyl C_2-C_6alkenyl C_2-C_6alkynyl C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C -C_4alkyl C -C_6alkoxy mono- and di(C_1-C_6alkyl)amino, amino(C_1-C_6)alkyl and mono- and di(C_1 C_6alkyl)amino, wherein in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula VIII is substituted

17 A compound or salt according to Claim 15 where n

R is selected from C -C_{10}alkyl and (C_3-C_7cycloalkyl)C_0-C_4alkyl each of which is substituted with 0 or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino

18 A compound or salt according to Claim 15 wherein

R is selected from C_{3-9}heterocycloalkyl and (C_{3-9}heterocycloalkyl)C_{1-4}alkyl, each of which is substituted with 0-4 substitutents selected from halogen, amino, hydroxy nitro, cyano C_1-C_6alkyl, C -C_6alkoxy C -C_6hydroxyalkyl C_1-C_6alkoxyC -C_6alkyl, (C C_6)haloalkyl (C_1-C_6)haloalkoxy mono- and d -(C_1-C_6)alkylamino XR_C

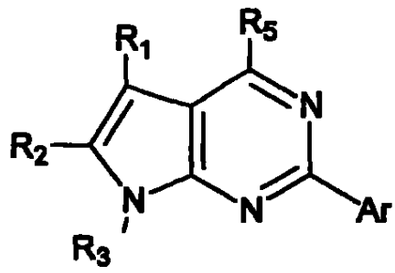
19 A compound or salt according to Claim 18 wherein

R is chosen from tetrahydrofuranyl tetrahydropyranyl morpholinyl pyrrolidinyl piperidinyl piperazinyl [2 2 1]-azabicyclic rings [2 2.2]-azabicyclic rings, [3 3 1] azabicyclic rings, quinuclidinyl azetidinyl azetidinonyl oxindolyl dihydroimidazolyl, and pyrrolidinonyl each of which is substituted with from 0 to 2 substituents independently chosen from

(i) halogen hydroxy amino cyano or

(ii) C_1-C_6alkyl C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino, each of which is substituted with 0 or 1 substituents selected from halogen hydroxy amino C_{1-2}alkoxy or C_{3-9}heterocycloalkyl

20 A compound or salt according to Claim 3 of Formula X



Formula X

wherein R_1 R_2, R_3 R_5 and Ar are as defined in Claim 3

21 A compound or salt according to Claim 20 wherein

R_1 is as defined for Claim 3

R_2 is selected from hydrogen, methyl, and ethyl

R_3 is selected from hydrogen and C -C_6alkyl

R_5 is selected from hydrogen, halogen, cyano, amino C -C_6alkyl, C_1-C_6alkoxy C_3-C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl, (C_3-C_7cycloalkyl)C_1-C_4alkoxy mono and di(C_1-C_6alkyl)amino, amino(C_1-C_6)alkyl, mono and di(C_1-C_6alkyl)amino(C_1-C_6)alkyl, halo(C_1-C_6)alkyl and halo(C_1-C_6)alkoxy and

Ar is selected from the group consisting of phenyl pyridyl and pyrimidinyl each of which is mono- di or trisubstituted with substituents independently chosen from halogen cyano nitro halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C -C_4alkyl, C_1-C_6alkoxy mono- and di(C_1-C_6alkyl)amino, amino(C_1-C_6)alkyl, and mono- and di(C_1-C_6alkyl)amino, wherein in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula X is substituted

22 A compound or salt according to Claim 20 wherein

R_1 is selected from C_1-C_{10}alkyl and (C_3-C_7cycloalkyl)C_0-C_4alkyl, each of which is substituted with 0 or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C -C_4alkoxy and mono- and di-(C_1-C_4)alkylamino

23 A compound or salt according to Claim 20 wherein

R_1 is selected from C_{3-9}heterocycloalkyl and (C_{3-9}heterocycloalkyl)C_{1-4}alkyl each of which is substituted with 0-4 substitutents selected from halogen amino, hydroxy nitro

cyano, C -C6alkyl, C1-C6alkoxy C -C6hydroxyalkyl C1-C6alkoxyC -C6alkyl (C1 C6)haloalkyl (C1-C6)haloalkoxy mono- and di-(C -C6)alkylamino, XRC

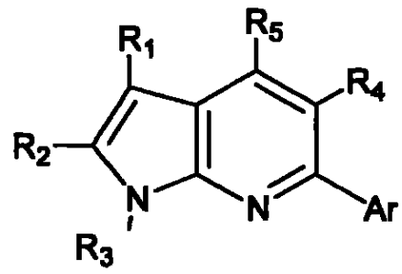
24 A compou d or salt according to Cla m 23 wherein

R1 is chosen from tetrahydrofuranyl tetrahydropyranyl morpholinyl pyrrolidinyl piperidinyl, piperazinyl [2 2 1]-azabicyclic rings, [2 2 2]-azabicyclic rings, [3.3 1] azabicyclic rings, quinuclid nyl azetidinyl azetidinonyl, oxindolyl dihydroimidazolyl and pyrrolidinonyl each of which is substituted with from 0 to 2 substituents independently chosen from

(i) halogen hydroxy amino cyano, or

(i) C1-C4alkyl C1-C4alkoxy and mono- and di-(C1-C4)alkylamino each of which is substituted with 0 or 1 substituents selected from halogen, hydroxy amino C1-2alkoxy or C3-9heterocycloalkyl

25 A ompo nd or salt accord g to Cla m 3 of Form la XII



Formula XII

wherein R1 R2, R3 R4, R5 and Ar are as defined in Cla m 3

.26 A compound or salt according to Claim 25 wherein

R1 is as defined for Claim 3

R2 is selected from hydrogen methyl and ethyl

R3 is selected from hydrogen and C1-C6alkyl

R4 and R5 are independently selected from hydrogen halogen, cyano, amino, C1-C6alkyl C1-C6alkoxy C3-C7cycloalkyl (C3-C7cycloalkyl)C1-C4alkyl (C3-C7cycloalkyl)C1 C4alkoxy mono and di(C1-C6alkyl)amino, amino(C1-C6)alkyl mono and di(C1-C6alkyl)amino(C1-C6)alkyl halo(C1-C6)alkyl and halo(C1-C6)alkoxy and

Ar is selected from the group consisting of phenyl pyridyl and pyrimidinyl each of which is mono- di or trisubstituted with substituents independently chosen from halogen,

cyano, nitro, halo(C -C_6)alkyl halo(C_1-C_6)alkoxy hydroxy amino, C -C_6alkyl, C_2-C_6alkenyl C_2-C_6alkynyl, C_3-C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl, C_1-C_6alkoxy mono- and di(C_1-C_6alkyl)amino, amino(C_1-C_6)alkyl, and mono- and di(C_1 C_6alkyl)amino, wherein, in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula XII is substituted

27 A compound or salt according to Claim 25 wherein

R_1 is selected from C_1-C_{10}alkyl and (C_3-C_7cycloalkyl)C_0-C_4alkyl, each of which is substituted with 0 or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino

28 A compound or salt according to Claim 25 wherein

R_1 is selected from C_{3-9}heterocycloalkyl and (C_{3-9}heterocycloalkyl)C_{1-4}alkyl, each of which is substituted with 0-4 substitutents selected from halogen, amino, hydroxy nitro, cyano, C_1-C_6alkyl C_1-C_6alkoxy C -C_6hydroxyalkyl, C_1-C_6alkoxyC_1-C_6alkyl, (C_1 C_6)haloalkyl (C_1-C_6)haloalkoxy mono- and di-(C_1-C_6)alkylamino, XR_C

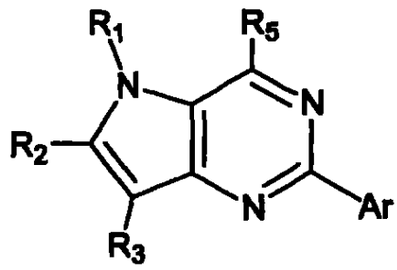
29 A compound or salt according to Claim 28, wherein

R_1 is chosen from tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl [2.2 1]-azabicyclic rings, [2.2.2]-azabicyclic rings, [3 3 1] azabicyclic rings, quinuclidinyl, azetidinyl, azetidinonyl, oxindolyl, dihydro midazolyl and pyrrolidinonyl, each of which is substituted with from 0 to 2 substituents independently chosen from

(i) halogen, hydroxy amino cyano, or

(ii) C_1-C_4alkyl, C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino, each of which is substituted with 0 or 1 substituents selected from halogen, hydroxy amino, C_{1-2}alkoxy or C_{3-9}heterocycloalkyl

30 A compound or salt according to Claim 3 of Formula XIV



Formula XIV

wherein R_1 R_2, R_3 R_5, and Ar are as defined in Claim 3

31 A compound or salt accord ng to Claim 30 wherein

R_1 is as defined for Claim 3

R_2 is selected from hydrogen, methyl, and ethyl

R_3 is C_1-C_3alkyl

R_5 is selected from hydrogen halogen cyano, amino, C_1-C_6alkyl C_1-C_6alkoxy C_3-C_7cycloalkyl (C -C_7cycloalkyl)C_1-C_4alkyl (C_3-C_7cycloalkyl)C -C_4alkoxy mono and di(C_1-C_6alkyl)amino amino(C_1-C_6)alkyl mono and di(C_1-C_6alkyl)amino(C -C_6)alkyl halo(C_1-C)alkyl and h lo(C -C_6)alkoxy and

Ar s selected from the group consisting of phenyl pyridyl and pyrimidinyl each of which s mono- di or trisubstituted with substituents independently chosen from halogen, cyano, nitro halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino, C_1-C_6alkyl C_2-C_6alkenyl C_2-C_6alkynyl C_3-C_7cycloalkyl (C_3-C_7cycloalkyl)C_1-C_4alkyl, C -C_6alkoxy mono- and d (C C_6alkyl)amino, amino(C_1-C_6)alkyl and mono- and di(C_1-C_6alkyl)amino wherein in Ar at least one of the positions ortho to the point of attachment of A shown in Formula XIV is substituted

32 A compound or salt according to Claim 30 wherein

R is selected from C_1-C $_0$alkyl and (C_3-C_7cycloalkyl)C_0-C_4alkyl each of wh ch is substituted with 0 or more substituents independently chosen from halogen hydroxy amino, oxo, cyano, C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino

33 A compound or salt according to Claim 30 wherein

R is selected from C_{3-9}heterocycloalkyl and (C_{3-9}heterocycloalkyl)C_{1-4}alkyl each of which is substituted with 0-4 substitutents selected from halogen amino, hydroxy nitro,

cyano, C_1-C_6alkyl, C -C_6alkoxy C_1-C_6hydroxyalkyl, C_1-C_6alkoxyC_1-C_6alkyl, (C_1 C_6)haloalkyl, (C_1-C_6)haloalkoxy mono- and di-(C_1-C_6)alkylamino XR_C

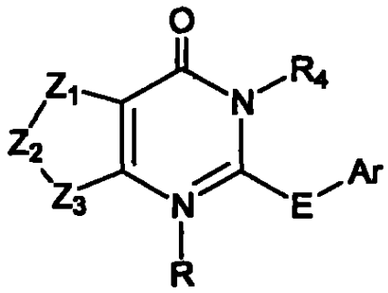
34 A compound or salt according to Claim 33 wherein

R_1 is chosen from tetrahydrofuranyl tetrahydropyranyl, morpholinyl pyrrolidinyl, piperidinyl, piperazinyl [2.2.1]-azabicyclic rings, [2.2.2]-azabicyclic rings, [3.3.1] azabicyclic rings, quinuclidinyl, azetidinyl, azetidinonyl, oxindolyl, dihydroimidazolyl, and pyrrolidinonyl each of which is substituted with from 0 to 2 substituents independently chosen from

(i) halogen, hydroxy amino, cyano, or

(ii) C_1-C_4alkyl, C_1-C_4alkoxy and mono- and di-(C_1-C_4)alkylamino, each of which is substituted with 0 or 1 substituents selected from halogen, hydroxy amino C_{1-2}alkoxy or C_{3-5}heterocycloalkyl

35 A compound of the Formula XX



Formula XX

or a pharmaceutically acceptable salt thereof, wherein

E is a single bond, O $S(O)_m$, NR_{10} or $CR_{10}R_{11}$

R_{10} and R_{11} are independently hydrogen or C_1-C_4 alkyl

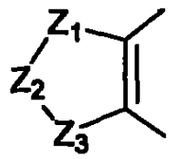
m is 0 1 or 2

Ar is chosen from

phenyl which is mono- di or tri-substituted, 1 naphthyl and 2 naphthyl, each of which is optionally mono- di or tri-substituted, and optionally mono- di or tri-substituted heteroaryl said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

R is oxygen or absent,

the group



represents a saturated, unsaturated or aromatic 5-membered ring system containing 0 or 1 heteroatoms, wherein

Z_1 is CR CR_1R_1 or NR_1

Z_2 is nitrogen oxygen sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen oxygen sulfur sulfoxide, sulfone, CR_3, CR_3R_3 or NR_3''

R_1 is chosen from halogen, hydroxy cyano, amino, optionally substituted alkyl, optionally substituted alkenyl optionally substituted alkynyl, optionally substituted alkoxy optionally substituted mono or dialkylamino optionally substituted (cycloalkyl)alkyl optionally substituted cycloalkyl optionally substituted heterocycloalkyl optionally substituted alkylthio optionally substituted alkylsulfinyl optionally substituted alkylsulfonyl optionally substituted mono- or dialkylcarboxamide, optionally substituted carbocyclic aryl and optionally substituted heteroaryl said optionally substituted heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

R_1 is chosen from optionally substituted alkyl optionally substituted alkenyl optionally substituted alkynyl optionally substituted (cycloalkyl)alkyl optionally substituted cycloalkyl optionally substituted heterocycloalkyl optionally substituted (heterocycloalkyl)alkyl optionally substituted carbocyclic aryl, and optionally substituted heteroaryl said optionally substituted heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and, in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

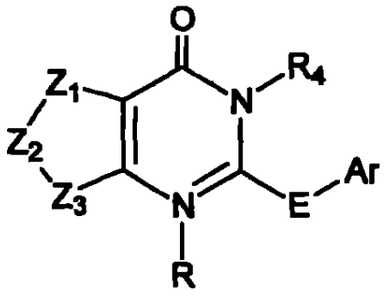
R_2 and R_3 are independently chosen from hydrogen halogen hydroxy amino, cyano, nitro alkyl haloalkyl alkoxy aminoalkyl, and mono and dialkylamino

R_1 R_2 and R_3 are independently chosen from hydrogen halogen alkyl haloalkyl and aminoalkyl

R_2 and R_3 are independently chosen from hydrogen alkyl haloalkyl and aminoalkyl and

R_4 is hydrogen, alkyl aminoalkyl and haloalkyl

36 A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

E is a single bond, O $S(O)_m$, NR_{10} or $CR_{10}R_{11}$

R_{10} and R_{11} are independently hydrogen or C_1-C_4 alkyl

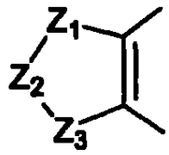
m is 0 1 or 2

R is oxygen or absent

Ar is chosen from

phenyl which is mono- di or tri -substituted 1 naphthyl and 2 naphthyl, each of which is optionally mono- di or tri substituted and optionally mono- di o tri -substituted heteroaryl, said heteroaryl having from 1 to 3 rings, 5 to 7 ring members in each ring and in at least one of said rings, from 1 to about 3 heteroatoms selected from the group consisting of N O and S

the group



represents a saturated, unsaturated or aromatic ring system comprising 0 or 1 heteroatoms, wherein

Z is CR_1 CR_1R_1 or NR_1

Z_2 is nitrogen, oxygen, sulfur CR_2, CR_2R_2 or NR_2

Z_3 is nitrogen, oxygen, sulfur sulfoxide sulfone CR_3, CR_3R_3 or NR_3

R_1 is chosen from

i) halogen, hydroxy cyano, amino C -C_{10}carbhydryl -O(C_1-C_6carbhydryl), mono or di(C_1 C_6carbhydryl)amino, (C_3-C_7cyclocarbhydryl)C_1-C_4carbhydryl, halo(C_1 C_6)carbhydryl, -O(halo(C -C_6)carbhydryl) and $S(O)_m$(C_1-C_6carbhydryl) -O(C_3-

C_7cyclocarbhydryl)C_1-C_4carbhydryl C_{3-9}heterocycloalkyl (C_{3-9}heterocycloalkyl)C_1 C_6alkyl and $S(O)_m$(C_1-C_6carbhydryl),

where each carbhydryl is independently straight, branched or cyclic, contains zero or 1 or more double or triple bonds,

where each heterocycloalkyl has 1 or 2 ring heteroatoms selected from N O or S and the point of attachment is carbon or nitrogen and

where each carbhydryl heterocycloalkyl or cyclocarbhydryl is optionally substituted by one or more substituents independently chosen from halogen hydroxy amino, oxo cyano C_1-C_6alkyl, C_1-C_6alkoxy haloC$_1$-C_6alkoxy C_1-C_6alkanoyl, C_1 C_6alkanoyloxy C -C_6alkoxycarbonyl N-(C_1-C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N (C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkoxycarbo yl)-N-(C_0-C_6alkyl)amino C_1-C_6alkylsulfonamide, C -C_6alkylsulfonyl C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C -C_6alkoxyC_1-C_6alkyl C -C_6haloalkoxy 5 to 7 membered heteroaryl 5 to 7 membered heterocycloalkyl mono- and di-(C_1-C_6)alkylamino, N (C -C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, mono- and di-(C_1 C_6)alkylcarbam yl XR_C nd X Z_4 and

ii) phenyl which s mono- di or tri substituted with R_A 1 naphthyl 2-naphthyl pyridyl dihydropyridyl, tetrahydropyridyl pyrimidinyl pyrazinyl pyridiz nyl thienyl thiazolyl oxazolyl, isoxazolyl, pyrrolyl furanyl and triazolyl each of which is optionally mono- di or tri-substituted with R_A

R_1 is chosen from C_1-C_{10}alkyl, C_2-C_{10}alkenyl C_2-C_{10}alkynyl, C_3-C_7cycloalkyl (C_3 C_7cycloalkyl)C_1-C_4alkyl C_{3-9}heterocycloalkyl (C_{3-9}heterocycloalkyl)C -C_4alkyl and halo(C_1-C_6)alkyl each of which is substituted with 0 or more substituents independently chosen from halogen, hydroxy amino, oxo, cyano, C_1-C_6alkyl C_1 C_6alkoxy haloC$_1$-C_6alkoxy C_1-C_6alkanoyl C_1-C_6alkanoyloxy C_1-C_6alkoxycarbonyl, N-(C -C_6alkanoyl)-N-(C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)amino, N-(C -C_6alkoxycarbonyl)-N (C_0-C_6alkyl)amino C_1 C_6alkylsulfonamide, C -C_6alkylsulfonyl C_1-C_6alkylsulfonyloxy C_1-C_6hydroxyalkyl C_1-C_6alkoxyC_1-C_6alkyl C_1-C_6haloalkoxy 5 to 7 membered heteroaryl 5 to 7 membered heterocycloalkyl mono- and di-(C_1-C_6)alkylamino, N-(C_1-C_6alkanoyl)-N (C_0-C_6alkyl)amino, N-(C_1-C_6alkanoyloxy)-N-(C_0-C_6alkyl)ammo, N-(C_1

C_6alkoxycarbonyl)-N-(C_0-C_6alkyl)amino, mono- and di-(C_1-C_6)alkylcarbamoyl, XR_C and X Z

R_2 and R_3 are independently chosen from hydrogen, halogen, hydroxy amino, cyano, nitro, C_1-C_6alkyl, halo(C_1-C_6)alkyl, C_1-C_6alkoxy amino(C_1-C_6)alkyl, and mono and di(C_1-C_6)alkylamino

R_2 and R_3 are independently chosen from hydrogen, halogen, C_1-C_6alkyl, halo(C_1-C_6)alkyl, and amino(C_1-C_6)alkyl

R_2 and R_3 are independently chosen from hydrogen, C_1-C_6alkyl halo(C -C_6)alkyl, and amino(C_1-C_6)alkyl

R_4 is hydrogen C -C_6alkyl, C -C_6aminoalkyl, and C_1-C_6haloalkyl

R_A is independently selected at each occurrence from halogen cyano nitro halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino, C_1-C_6alkyl substituted with 0-2 R_B, C_2-C_6alkenyl substituted with 0-2 R_B, C_2-C_6alkynyl substituted with 0-2 R_B, C_3-C_7cycloalkyl substituted with 0-2 R_B, (C_3-C_7cycloalkyl) C_1-C_4alkyl substituted with 0-2 R_B, C C_6alkoxy substituted with 0-2 R_B, NH(C_1-C_6alkyl) substituted with 0-2 R_B, N(C_1 C_6alkyl)(C_1-C_6alkyl) each C_1-C_6alkyl independently substituted w th 0-2 R_B, XR_C and Y

R_B is independently selected at each occurrence from the group consisting of halogen, hydroxy cyano amino C_1-C_4alkyl -O(C -C_4alkyl) NH(C_1-C_4alkyl) N(C_1 C_4alkyl)(C -C_4alkyl), $S(O)_n$(alkyl) halo(C_1-C_4)alkyl halo(C -C)alkoxy CO(C_1 C_4alkyl), CONH(C_1-C_4alkyl) CON(C_1-C_4alkyl)(C_1-C_4alkyl), XR_C and Y

R_C and R_D, which may be the same or different, are independently selected at each occurrence from.

hydrogen, and

straight, branched, or cyclic alkyl groups, including (cycloalkyl)alkyl groups consisting of 1 to 8 carbon atoms, which straight, branched, or cycl c alkyl groups contain zero or one or more double or triple bonds, each of which 1 to 8 carbon atoms may be further substituted with one or more substituent(s) independently selected from oxo, hydroxy halogen, cyano amino C_1-C_6alkoxy NH(C_1-C_6alkyl), N(C_1 C_6alkyl)(C_1-C_6alkyl), NHC(=O)(C_1-C_6alkyl), N(C_1-C_6alkyl)C(=O)(C_1-C_6alkyl) $NHS(O)_n$(C_1-C_6alkyl), $S(O)_n$(C_1-C_6alkyl), $-S(O)_nNH$(C_1-C_6alkyl) $S(O)_nN$(C_1 C_6alkyl)(C -C_6alkyl), and Z,

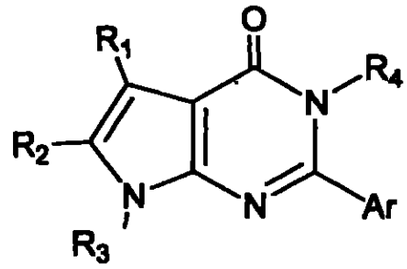
X is independently selected at each occurrence from the group consisting of -CH_2- -CHR_D- O- -C(=O)- -C(=O)O- -S(O)$_n$ NH NR_D- -C(=O)NH -C(=O)NR_D- -S(O)$_n$NH -S(O)$_n$$NR_D$- -OC(=S)S- NHC(=O) NR_DC(=O)- NHS(O)$_n$ -OSiH$_2$- -OSiH(C C_4alkyl)- -OS (C_1-C_4alkyl)(C -C_4alkyl) and –NR_DS(O)$_n$

Y and Z are independently selected at each occurrence from 3 to 7 membered carbocyclic or heterocyclic groups which are saturated, unsaturated, or aromatic which may be further substituted with one or more substituents independently selected from halogen oxo hydroxy amino cyano C_1 C_4alkyl -O(C_1-C_4alkyl) -C(O)(C_1-C_4alkyl), NH(C_1-C_4alkyl) N(C_1-C_4alkyl)(C_1-C_4alkyl) nd S(O)$_n$(alkyl),

wherein said 3 to 7 memberered heterocyclic groups conta n one or more heteroatom(s) independently selected from N O and S with the point of attachment being either carbon or nitrogen and

n is independently selected at each occurrence from 0 1 and 2

37 A compo nd or salt according to Cl im 36 of Formula XXI



Formula XXI

where n,

R_1 R_2 R_3 R_4 re as defined i Claim 37 and

Ar is chosen from

phenyl which is mono- di or tri-substituted with R_A and 1 naphthyl 2 naphthyl, pyridyl and pyrimidinyl pyrimidinyl pyrazinyl pyridizinyl thienyl thiazolyl oxazolyl isoxazolyl, pyrrolyl furanyl and triazolyl each of which is optionally mono- di or tri-substituted with R_A

38 A compound or salt according to Claim 37 wherein

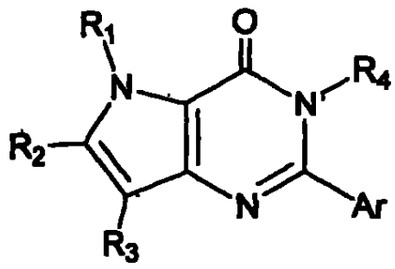
R is as defined in Claim 36

R_2 and R_4 are independently selected from hydrogen, methyl and ethyl

R_3 is selected from hydrogen and C_1-C_6alkyl and

Ar is selected from the group consisting of phenyl, pyridyl and pyrimidinyl each of which is mono- di or trisubstituted with substituents independently chosen from halogen, cyano nitro, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino, C_1-C_6alkyl C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl C_1-C_6alkoxy mono- and di(C_1-C_6alkyl)amino, amino(C_1-C_6)alkyl, and mono- and di(C_1-C_6alkyl)amino, wherein in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula XXI is substituted

39 A compound or salt according to Claim 36 of Formula XXII



Formula XXII

where in R_1 R_2, R_3 R_4 and R_5 are as defined in Claim 36 and

Ar is chosen from

phenyl which is mono- di or tri-substituted with R_A, and 1 naphthyl, 2-naphthyl, pyr dyl and pyrimidinyl pyrimidinyl, pyrazinyl, pyridizinyl, thienyl, thiazolyl, oxazolyl, isoxazolyl, pyrrolyl, furanyl, and triazolyl each of which is optionally mono- di or tri-substituted with R_A

40 A compound or salt according to Claim 39 wherein

R_1 is as defined in Claim 39

R_2 and R_4 are independently selected from hydrogen, methyl and ethyl

R_3 is selected from hydrogen and C_1-C_6alkyl and

Ar is selected from the group consisting of phenyl, pyridyl and pyrimidinyl each of which is mono- di- or trisubstituted with substituents independently chosen from halogen, cyano nitro halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy hydroxy amino C_1-C_6alkyl, C_2-C_6alkenyl C_2-C_6alkynyl, C_3-C_7cycloalkyl, (C_3-C_7cycloalkyl)C_1-C_4alkyl, C_1-C_6alkoxy mono- and di(C -C_6alkyl)amino, amino(C -C_6)alkyl, and mono- and di(C_1

C_6alkyl)amino, wherein in Ar at least one of the positions ortho to the point of attachment of Ar shown in Formula XXII is substituted

41 A compound or pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of

5-(1 Ethyl propyl)-2-(2 methoxy-4-trifluoromethoxy phenyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyrazine

{4 Ethyl 5 [5-(1-ethyl propyl)-3 7-dimethyl 5H pyrrolo[2,3-b]pyrazin 2 yl] pyridin 2 yl} dimethyl-amine

{3 Bromo-4-ethyl 5 [5-(1-ethyl-propyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyrazin 2 yl] pyridin 2 yl}-ethyl methyl-amine

Ethyl-{4-ethyl 5-[5-(1-ethyl-propyl)-3 7-d methyl-5H-pyrrolo[2 3-b]pyrazin 2 yl] pyridin 2 yl} methyl-amine

{5 [5-(1 Ethyl-propyl)-3 7-dimethyl 5H pyrrolo[2 3 b]pyrazin 2 yl]-4-methoxy-pyridin 2 yl}-dimethyl-amine

2 [2 Ethoxy 5-methanes lfonyl-6-(1 methyl but 3-enyl)-pyridin 3 yl] 5-(1-ethyl propyl)-3 7-dimethyl 5H-pyrrolo[2 3 b]pyrazine

2-(2 Ethoxy-6-ethyl 5-methanesulfonyl pyridi 3 yl) 5-(1-ethyl propyl)-3 7-d methyl 5H pyrrolo[2,3-b]pyrazine

{5 [3-Chloro-5-(1-ethyl propyl)-7 methyl 5H pyrrolo[2,3 b]pyrazin-2 yl]-4-ethyl pyridin 2 yl}-ethyl methyl-amine

{5 [3-Chloro-5-(1-ethyl propyl) 7 methyl 5H pyrrolo[2,3 b]pyrazin 2-yl]-4-ethyl pyridin 2 yl}-dimethyl-amine

{5-[3-Chloro-5-(1-ethyl propyl)-7 methyl 5H pyrrolo[2,3 b]pyrazin 2 yl]-4-ethyl pyridin 2 yl}-diethyl-amine

3-Chloro-5-(1-ethyl-propyl) 2-(3 isopropyl 5 methoxy-2,3-dihydro-furo[3,2 b]pyridin-6-yl) 7 methyl 5H-pyrrolo[2,3 b]pyrazine

3-Chloro-5-(1-ethyl-propyl)-2-(3 isopropyl 5 methoxy-furo[3 2 b]pyridin 6-yl) 7 methyl 5H-pyrrolo[2,3 b]pyrazine

(R)-2 [2-(6 Isopropyl 2-methoxy pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin-5 yl] 3 methoxy propan 1-ol

5-(1 Ethyl propyl) 2-(6-isopropyl 2 methoxy pyridin 3 yl) 3 7-dimethyl 5H pyrrolo[2,3 b]pyrazine

2-(2 Ethyl-6-isopropyl-pyridin 3 yl)-5-(1-ethyl propyl)-3 7-dimethyl 5H-pyrrolo[2,3 b]pyrazine

2 [(S)-2 (6-Isopropyl-2 methoxy pyridin-3 yl)-3 7-dimethyl pyrrolo[2,3-b]pyrazin 5 yl] butan 1-ol

Methanesulfonic acid 2-[(S)-2-(6-isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3-b]pyrazin-5-yl]-butyl ester

3 {2 [(S) 2-(6-Isopropyl 2 methoxy-pyridin-3 yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin 5 yl]-butyl}-oxazolidin-2-one

(S) 2-(6-Isopropyl 2-methoxy-pyridin-3 yl)-5-(1 methoxymethyl-propyl)-3 7-dimethyl-5H pyrrolo[2 3 b]pyrazine

Ethyl {2 [(S)-2-(6-isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl-pyrrolo[2,3 b]pyrazin-5 yl] butyl} methyl-amine

{2 [(S)-2-(6-Isopropyl-2-methoxy-pyridin-3-yl)-3 7-dimethyl-pyrrolo[2,3-b]pyrazin-5-yl]-butyl}-methyl-amine

N {2 [(S) 2-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl-pyrrolo[2 3 b]pyrazin 5 yl] butyl} N methyl methanesulfonamide

N {2-[(S) 2 (6 Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin 5 yl] butyl} N methyl-acetamide

{2 [(S)-2-(6-Isopropyl 2-methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3-b]pyrazin-5 yl]-butyl} methyl-carbamic acid methyl ester

(R)-2-(6-Isopropyl-2 methoxy pyridin 3 yl)-5-(1 methoxymethyl propyl) 3 7-dimethyl-5H-pyrrolo[2 3 b]pyrazine

Acetic acid 2 [(R) 2-(6-isopropyl-2-methoxy-pyridin 3-yl)-3 7-dimethyl-pyrrolo[2 3 b]pyrazin-5 yl]-butyl ester

2 [(R)-2-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl-pyrrolo[2 3 b]pyrazin 5 yl] butan 1-ol

(R)-2-(2 Ethyl-6-isopropyl-pyridin-3 yl)-5 (1-methoxymethyl-propyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyrazine

{6-Isopropyl 3-[(R)-5-(1 methoxymethyl-propyl)-3 7-dimethyl-5H pyrrolo[2,3 b]pyrazin 2 yl] pyridin 2 yl}-methyl-amine

{2 [(R)-2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin 5 yl]-butyl}-dimethyl-amine

(R)-2-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl 5-(1 pyrrolidin 1 ylmethyl propyl)-5H-pyrrolo[2,3-b]pyrazine

Diethyl {2 [(R) 2-(6-isopropyl 2-methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin-5 yl]-butyl}-amine

Isopropyl {2-[(R)-2-(6 isopropyl 2 methoxy-pyrid n 3 yl)-3 7-dimethyl pyrrolo[2,3 b]pyrazin 5 yl]-butyl} methyl-amine

(R)-2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl 5-(1 morpholin-4-ylmethyl propyl) 5H pyrrolo[2 3 b]pyrazine,

Cyclobutyl {2 [(R)-2 (6-isopropyl-2 methoxy pyridin 3 yl) 3 7-dimethyl-pyrrolo[2,3 b]pyrazin-5 yl]-butyl} amine

{2 [(R)-2-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin-5 yl] butyl}-(2 methoxy-ethyl)-methyl-amine

2-(6-Isopropyl 2-methoxy pyridin-3 yl)-3 7 dimethyl 5-(1 methylene-propyl)-5H pyrrolo[2,3 b]pyrazine

Butyl-ethyl {2 [(R) 2 (6 isopropyl 2 methoxy pyr din 3 yl) 3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl] butyl}-amine

5-sec-Butyl-2-(6- sopropyl-2-methoxy pyrid n 3 yl)-3 7-d methyl 5H pyrrol [2,3 b]pyrazine

Dimethyl-carbamic acid 2 [(R)-2-(6-isopropyl 2 methoxy pyridin 3 yl) 3 7-dimethyl pyrrolo[2,3-b]pyrazin-5 yl]-butyl ester

{2 [(R)-2-(6-Isopropyl 2 methoxy pyrid n 3 yl)-3 7-dimethyl pyrrolo[2 3 b]pyrazin 5 yl] butyl}-dipropyl-amine

2-(6-Isopropyl 2-methoxy pyridin 3 yl)-3 7-dimethyl 5 [(R)-1-(4-methyl-piperazin 1 ylmethyl)-propyl] 5H pyrrolo[2,3 b]pyraz ne

1-(4-{(R)-2-[2-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 7-dimethyl-pyrrolo[2,3 b]pyrazin 5 yl]-butyl} piperazin-1 yl)-ethanone

2-(2-Ethyl-6-isopropyl pyridin 3 yl)-3 7-dimethyl 5-((R)-1-morpholin-4-ylmethyl propyl) 5H-pyrrolo[2,3 b]pyrazine

{3-[3 7 Dimethyl-5-((R) 1 morpholin-4 ylmethyl propyl)-5H pyrrolo[2 3 b]pyrazin 2-yl]-6-isopropyl pyridin 2 yl} methyl-amine

{(R)-2 [2-(4-Difluoromethoxy 2 methoxy phenyl)-3 7-dimethyl pyrrolo[2,3-b]pyrazin 5 yl]-butyl}-ethyl methyl-amine

{(R)-2 [2-(2-Chloro-4-methoxy phenyl) 3 7-dimethyl-pyrrolo[2 3-b]pyrazin-5 yl] butyl} ethyl-methyl-amine

5-Isopropyl-2 (6-isopropyl-2-methoxy pyridin 3 yl)-3 7-dimethyl-5H-pyrrolo[2 3 b]pyrazine

[6-Isopropyl 3-(5-isopropyl 3 7-dimethyl 5H pyrrolo[2,3-b]pyrazin 2 yl)-pyridin 2 yl] methyl-amine

2-(2 Ethyl-6-isopropyl pyridin-3 yl)-5 isopropyl 3 7-dimethyl 5H-pyrrolo[2 3 b]pyrazine

2-(4-Difluoromethoxy 2 methoxy phenyl)-5 isopropyl 3 7-dimethyl 5H-pyrrolo[2,3 b]pyrazine

5 Isopropyl 2-(2 methoxy-4-trifluoromethyl-phenyl)-3 7-dimethyl 5H pyrrolo[2,3-b]pyrazine

[3-(3 7 D methyl 5-propyl 5H pyrrolo[2,3-b]pyrazin 2 yl)-6-isopropyl-pyridin-2 yl] methyl-amine

2-(6-Isopropyl 2-methoxy-pyridin 3 yl)-3 7-dimethyl 5-propyl 5H-pyrrolo[2,3-b]pyrazine

5 Isopropyl 2-(2 methoxy-4-trifluoromethoxy ph nyl)-3 7-dimethyl-5H pyrrolo[2 3 b]pyrazine

2-(2 Ethyl-6-isopropyl pyridin 3-yl)-3 7-d methyl 5-propyl 5H pyrrolo[2 3 b]pyrazine

(R)-2-(6-Isopropyl pyridin 3 yl)-5 (1-methoxymethyl propyl)-3 7-dimethyl 5H pyrrolo[2 3 b]pyrazine

(S) 2-(2 Ethyl-6 isopropyl-pyridin 3 yl)-5-(1 methoxymethyl-propyl)-3 7-dimethyl-5H pyrrolo[2 3-b]pyrazine

{6-Isopropyl 3 [(S)-5-(1 methoxymethyl-propyl) 3 7-dimethyl 5H pyrrolo[2,3 b]pyrazin 2 yl]-pyridin 2 yl}-methyl-amine

(S)-3-Chloro-2-(6-isopropyl 2 methoxy pyridin-3 yl)-5-(2-methoxy-1-methyl-ethyl)-7 methyl 5H-pyrrolo[2 3 b]pyrazine

(S)-3 Ethyl 2-(6-isopropyl 2-methoxy-pyridin 3 yl)-5-(2 methoxy 1 methyl-ethyl)-7 methyl 5H-pyrrolo[2 3 b]pyrazine

{3 [3 Ethyl 5-((S)-2-methoxy-1-methyl-ethyl)-7 methyl-5H pyrrolo[2,3 b]pyrazin 2 yl] 6-isopropyl-pyridin-2 yl} methyl-amine

{3 [3-Chloro-5-((S)-2 methoxy 1 methyl-ethyl)-7 methyl 5H-pyrrolo[2 3-b]pyrazin 2 yl]-6-isopropyl pyridin-2 yl}-methyl-amine

{6-Isopropyl 3 [5-((R)-1 methoxymethyl-propyl)-3 7-dimethyl-5H pyrrolo[2,3 b]pyrazin-2 yl] pyridin 2 yl}-dimethyl-amine

3-Chloro-2-(6-isopropyl 2 methyl-pyridin 3 yl)-5-((S)-2-methoxy 1-methyl-ethyl)-7 methyl 5H pyrrolo[2,3 b]pyrazine

5-((R)-1 Ethoxymethyl propyl) 2-(6 isopropyl 2 methoxy-pyridin 3 yl)-3 7-dimethyl 5H-pyrrolo[2 3-b]pyrazine

2-(6-Isopropyl 2 methyl-pyridin 3 yl)-5-((R)-1 methoxymethyl propyl)-3 7-dimethyl 5H pyrrolo[2 3 b]pyrazine

{3 [5-((R)-1 Ethoxymethyl propyl)-3 7-dimethyl-5H-pyrrolo[2 3-b]pyrazin-2 yl]-6-isopropyl-pyridin 2-yl} methyl-amine

Ethyl {6-isopropyl 3 [5-((R)-1 methoxymethyl-propyl)-3 7-dimethyl 5H pyrrolo[2,3 b]pyrazin-2 yl]-pyrid n 2 yl}-am ne

1-(1 Ethyl propyl)-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

Ethyl {4-ethyl 5 [1-(1-ethyl propyl)-3 6-dimethyl 1H-pyrrolo[3 2 b]pyrid 5 yl] pyridin 2 yl} methyl-amine

1-(1 Ethyl propyl) 5-(6-isopropyl 2-methoxy pyridin 3 yl)-3 6-dimethyl 1H-pyrrolo[3 2 b]pyridine

5-(2 Ethyl-6-isopropyl pyridin-3 yl)-1 (1-ethyl propyl)-3 6-dimethyl 1H-pyrrolo[3 2 b]pyridine

{4-Ethyl 5 [1-(1-ethyl propyl)-3 6-dimethyl 1H-pyrrolo[3 2 b]pyridin 5 yl] pyridin 2 yl}-dimethyl-amine

{3 [1-(1 Ethyl propyl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridin-5 yl]-6-isopropyl-pyridin 2 yl}-methyl-amine

1-sec Butyl 5-(2 methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

1-sec Butyl 5-(6-isopropyl 2 methoxy pyrid n 3 yl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

1-(2 Methoxy-1 methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridine

5-(6 Isopropyl 2-methoxy pyridin 3 yl) 1-(2 methoxy 1-methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridine

1 sec-Butyl 5-(2-ethyl-6-isopropyl-pyrid n 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

[3-(1-sec-Butyl 3 6-dimethyl-1H pyrrolo[3,2-b]pyridin 5 yl)-6-isopropyl-pyridin-2-yl] methyl-amine

5-(2 Ethyl-6-isopropyl pyridin-3 yl)-1-(2 methoxy-1-methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine

{6-Isopropyl-3 [1-(2-methoxy 1 methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridin 5 yl]-pyridin 2 yl} methyl-amine

1-Isopropyl-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

1 Isopropyl-5-(6-isopropyl-2 methoxy-pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

[6-Isopropyl 3-(1 isopropyl 3 6-dimethyl-1H-pyrrolo[3,2-b]pyridin-5 yl)-pyridin 2 yl] methyl-amine

5-(2 Ethyl-6-isopropyl-pyridin 3 yl)-1 isopropyl 3 6-dimethyl-1H-pyrrolo[3,2 b]pyridine

1-sec-Butyl-6-ethyl-5-(6 isopropyl 2 methoxy pyridin 3 yl)-3-methyl-1H pyrrolo[3 2 b]pyridine

1-(2-Fluoro-ethyl)-5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridine

1-[5-(6 Isopropyl-2 methoxy pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin-1-yl] ethanone

[5-(6-Isopropyl 2-methoxy py din 3 yl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin 1 yl]-acetic acid ethyl ester

1 Ethyl 5-(6-isopropyl 2-methoxy-pyridin-3-yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

2 [5-(6-Isopropyl 2-methoxy-pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl] propionic acid ethyl ester

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1,3 6-trimethyl 1H pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-(2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

2 [5-(6-Isopropyl 2-methoxy-pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl] propionic acid tert-butyl ester

1 Ethyl 5-(2-ethyl-6-isopropyl pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

[3-(1 Ethyl 3 6-dimethyl 1H-pyrrolo[3,2 b]pyridin 5 yl)-6-isopropyl pyridin 2 yl] methyl-amine

5-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1-propyl-1H-pyrrolo[3 2 b]pyrid ne

1-(2-Ethoxy-ethyl)-5-(6 isopropyl 2 methoxy-pyridin 3 yl)-3 6-d methyl 1H pyrrolo[3 2 b]pyridine

5-(2 Ethyl-6 isopropyl pyridin 3 yl)-1-(2 fluoro-ethyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine

{3 [1 (2 Fluoro-ethyl)-3 6-d methyl 1H pyrrolo[3,2-b]pyridin-5 yl]-6 isopropyl-pyridin 2 yl} methyl-amine

2 [5-(6 Isopropyl 2-methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin-1 yl] ethanol

2 [5-(6-Isopropyl 2 methoxy-pyridin-3 yl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin-1 yl] N methyl propion mide

5-(2 Ethyl-6- sopropyl pyrid 3 yl)-3 6-d methyl 1 propyl 1H pyrrolo[3 2 b]pyridine

1 Isobutyl 5 (6 isopropyl 2-methoxy pyridin 3 yl)-3 6-dimethyl-1H-pyrrolo[3 2 b]pyrid ne

1-Cyclopropylmethyl 5-(6- sopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyrid ne

Ethyl-[6-isopropyl 3-(1 sopropyl-3 6-dimethyl-1H pyrrolo[3,2-b]pyridin-5-yl)-pyridin 2 yl]-amine

[3-(3 6-Dimethyl 1 propyl 1H pyrrolo[3 2 b]pyridin 5 yl)-6-isopropyl-pyrid n 2 yl] methyl-amine

[3-(3 6-Dimethyl 1 propyl 1H pyrrolo[3,2 b]pyridin 5 yl)-6-isopropyl pyridin 2 yl] ethyl-amine

1-(3 Fluoro-propyl) 5-(6-isopropyl-2 methoxy pyridin-3-yl)-3 6-d methyl-1H pyrrolo[3 2 b]pyrid ne

1 [2-(2 Fluoro-ethoxy)-ethyl] 5-(6-isopropyl 2 methoxy pyridin 3 yl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine,

5-(2 Ethyl 6 sopropyl pyridin-3 yl)-1-(3 fluoro-propyl)-3 6-dimethyl 1H-pyrrolo[3 2 b]pyridine

{3 [1 (3 Fluoro-propyl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-methyl-amine

5-(6-Isopropyl 2-methoxy-pyridin 3 yl) 1-(3 methoxy-propyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

{6-Isopropyl 3-[1-((S)-2 methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-pyridin 2 yl} methyl-amine

5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridine

[3-(1 Isobutyl-3 6-dimethyl 1H-pyrrolo[3,2-b]pyridin 5 yl)-6-isopropyl-pyridin 2 yl]-methyl-amine

5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1 isobutyl-3 6-dimethyl-1H-pyrrolo[3,2 b]pyridine

1 Butyl-5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1-(2 morpholin-4-yl-ethyl)-1H pyrrolo[3,2 b]pyridine

1 Allyl-5-(6 isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine

[3-(1 Butyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyridin-5 yl)-6-isopropyl pyridin 2 yl] methyl-amine

1 Butyl-5-(2-ethyl-6-isopropyl pyridin 3 yl)-3 6-dimethyl-1H-pyrrolo[3 2-b]pyridine

(R)-2 [5-(6-Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] propan 1-ol

{6-Isopropyl 3 [1-((R) 2-methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-pyridin-2 yl} methyl-am ne

5-(2 Ethyl-6-isopropyl pyridin 3 yl) 1-((R)-2-methoxy-1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridine

5-(6-Isopropyl-2-methoxy-pyridin 3 yl)-1-((R)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H-pyrrolo[3,2-b]pyridine

1-((R)-2 Fluoro-1 methyl-ethyl)-5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H-pyrrolo[3,2-b]pyridine

5-(6-Isopropyl 2-methoxy-pyridin-3 yl)-3 6-dimethyl 1 (2-methyl-allyl)-1H pyrrolo[3 2 b]pyridine

[3-(1 Allyl-3 6-dimethyl-1H pyrrolo[3,-b]pyridin 5 yl)-6-isopropyl-pyridin 2 yl] methyl-amine

1 Allyl-5-(2-ethyl-6-isopropyl-pyridin-3 yl)-3 6-dimethyl-1H-pyrrolo[3 2-b]pyridine

5-(6-Isopropyl pyridin 3 yl)-3 6-dimethyl 1 propyl 1H-pyrrolo[3,2 b]pyridine

(S)-2 [5-(6-Isopropyl-2 methoxy pyr din-3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl]-3-methoxy propan-1-ol

1-((R)-1 Fluoromethyl 2 methoxy-ethyl)-5-(6 isopropyl 2-methoxy-pyrid n 3 yl)-3 6 dimethyl-1H pyrrolo[3,2-b]pyridine

{3 [1-((R)-1 Fluoromethyl 2-methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-methyl-amine,

5-(2 Ethyl-6-isopropyl-pyridin-3 yl)-1-((R)-1 fluoromethyl 2 methoxy-ethyl)-3 6 dimethyl 1H pyrrolo[3 2 b]pyridine

1-((R)-1 Fluoromethyl 2-methoxy-ethyl)-5-(6 isopropyl pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-(1-methoxymethyl butyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

{5 Bromo-6- sopropyl 3 [1-((S)-2 methoxy-1-methyl-ethyl) 3 6-dimethyl-1H pyrrolo[3,2 b]pyridin 5 yl] pyridin 2 yl} methyl-amine

{5 Ethyl 6-isopropyl 3 [1 ((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl] pyridin 2 yl} methyl-amine

1-((S)-1 Fluoromethyl-propyl)-5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

1-((R) 1 Fluoromethyl propyl) 5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

{3 [1-((S)-1 Fl oromethyl propyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl-pyridin-2 yl}-methyl-amine,

(S)-3 [5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2-b]pyridin 1 yl] 4-methoxy butyronitrile

(R)-2 [5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 6-d methyl pyrrolo[3,2-b]pyridin-1 yl] pentan 1-ol

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-((R)-1 methoxymethyl butyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

1-((R)-1 Fluoromethyl butyl)-5-(6- sopropyl 2 methoxy pyrid n 3 yl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2-methoxy-pyridin 3 yl)-1-(1 methoxymethyl inyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

{6-Isopropyl 3 [1-((R)-1 methoxymethyl-butyl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridin-5 yl] pyridin 2 yl} methyl amine,

5-(2 Ethyl-6-isopropyl-pyridin 3-yl)-1-((R)-1 methoxymethyl-butyl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine

(S)-2 [6-Ethyl 5-(6-isopropyl-2 methoxy-pyridin 3 yl)-3 methyl-pyrrolo[3,2 b]pyridin 1 yl]-3 methoxy-propan 1-ol

6-Ethyl 1-((R)-1 fluoromethyl 2-methoxy-ethyl)-5-(6-isopropyl 2 methoxy pyridin-3 yl)-3-methyl 1H-pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-1-(2-methoxy 1-methoxymethyl-ethyl)-3 6-dimethyl 1H-pyrrolo[3,2-b]pyridine

5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1-((S)-1 fluoromethyl-propyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

1-((S)-1 Fluoromethyl-propyl)-5-(6-isopropyl-pyridin 3 yl)-3 6-dimethyl-1H-pyrrolo[3,2 b]pyridine

{6-Isopropyl 3 [1-(2 methoxy 1-methoxymethyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridin 5 yl] pyridin 2 yl}-methyl-amine

1-((S)-1 Ethoxymethyl-propyl)-5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H-pyrrolo[3 2-b]pyridine

(R)-2 [5-(6-Isopropyl 2 methoxy-pyridin-3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin-1 yl]-3-methoxy propan-1-ol

1-((S)-1 Fluoromethyl 2 methoxy-ethyl)-5-(6-isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

{3 [1-((S)-1 Fluoromethyl 2-methoxy-ethyl)-3 6-dimethyl 1H-pyrrolo[3,2-b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-methyl-amine

6-Ethyl 1 isopropyl-5-(6-isopropyl 2-methoxy-pyridin 3 yl)-3 methyl 1H pyrrolo[3 2 b]pyridine

[3-(6-Ethyl 1 isopropyl 3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl)-6 isopropyl-pyridin-2 yl]-methyl-amine

6-Ethyl 5-(2-ethyl-6-isopropyl pyridin 3-yl)-1 isopropyl 3 methyl 1H-pyrrolo[3,2 b]pyridine

5-(2 Ethyl-6-isopropyl pyridin 3 yl)-1-(2 methoxy 1-methoxymethyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridine

{3-[1-((S)-1 Ethoxymethyl propyl) 3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl-pyridin 2 yl} methyl-amine,

2,5 Diethyl-6-[1-(1-ethyl propyl)-3 6-d methyl-1H pyrrolo[3 2 b]pyridm 5 yl] 3 sopropyl 3H imidazo[4 5 b]pyridine

(S)-2 [5-(2 Methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin-1 yl] butan 1-ol

1-((S)-1 Methoxymethyl propyl)-5 (2-methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl-1H pyrrolo[3 2-b]pyridine

1-((S)-1-Chloromethyl propyl) 5-(2 methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridme

1-((S)-2 Methoxy 1-methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6 dimethyl 1H pyrrolo[3 2 b]pyridine

5-(2 Methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

5-(2 Methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl 1-((S)-1 morpholin-4-ylmethyl propyl) 1H pyrrolo[3 2 b]pyrid e

{(S) 2 [5 (2 Methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl pyrrolo[3 2-b]pyridin 1 yl] butyl}-dimethyl-am ne

5-(2-Methoxy-4 trifluoromethoxy-phenyl)-3 6-d methyl 1-((S)-1-pyrrolid n 1 ylmethyl-propyl)-1H pyrrolo[3 2 b]pyridine

(S)-2 [5-(6 Isopropyl 2 methoxy-pyrid n 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin-1 yl] butan 1-ol

5 (6-Isopropyl 2 methoxy pyridin 3 yl)-1-((S)-1 methoxymethyl propyl) 3 6-dimethyl 1H-pyrrolo[3 2-b]pyridine

Methanesulfonic acid (S)-2 [5-(6- sopropyl 2-methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3 2-b]pyrid n 1 yl] butyl ester

{(S) 2 [5 (6-Isopropyl-2 methoxy-pyridin 3 yl)-3 6-d methyl-pyrrolo[3 2 b]pyridin 1 yl]-butyl}-dimethyl amine

(2R,6S) 2 6 Dimethyl morpholine-4-carboxylic acid 2 [5-(2 methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin 1 yl] butylester

Piperidine-1-carboxylic ac d (S)-2 [5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl pyrrolo[3 2 b]pyrid n 1 yl] butyl ester

4 Methyl piperazine 1-carboxylic acid (S)-2 [5-(2-methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] butyl ester

Azepane-1-carboxylic acid (S)-2 [5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-d methyl pyrrolo[3,2-b]pyridin 1 yl] butyl ester

4-Acetyl piperazine-1-carboxylic acid (S)-2 [5-(2-methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3 2 b]pyridin 1 yl] butyl ester

Ethyl-methyl-carbamic acid (S)-2-[5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl]-butyl ester

Diethyl-carbamic acid (S)-2 [5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl]-butyl ester

Ethyl-(2 methoxy-ethyl)-carbamic acid (S)-2 [5-(2 methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin-1 yl]-butyl ester

(2 Methoxy-ethyl)-carbamic acid (S)-2-[5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl]-butyl ester

Cyclopentyl-carbamic acid (S)-2 [5-(2-methoxy-4-trifluoromethoxy phenyl)-3 6-d methyl pyrrolo[3,2-b]pyridin 1 yl]-b tyl ester

1 [(S)-1-((2S 6R)-2,6-Dimethyl morpholin-4 ylmethyl)-propyl] 5-(2 methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl-1H-pyrrolo[3,2-b]pyridine

5-(2 Methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl 1-((S)-1-piperidin 1 ylmethyl propyl)-1H pyrrolo[3,2-b]pyridine

1-((S)-1 Methanesulfonylmethyl propyl)-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridine

5-(2 Methoxy-4 trifluoromethoxy-phenyl)-3 6-dimethyl 1 [(S) 1-(4 methyl-piperazin 1 ylmethyl)-propyl] 1H pyrrolo[3,2-b]pyridine

1-((S)-1 Azepan 1 ylmethyl-propyl)-5-(2 methoxy-4-trifluoromethoxy-phenyl) 3 6-dimethyl 1H-pyrrolo[3,2-b]pyridine

Methanesulfonic acid (S)-2 [5-(2-methoxy-4-trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] butyl ester

5-(6-Isopropyl 2 methoxy-pyridin-3-yl)-3 6-dimethyl 1-((S)-1-morpholin-4 ylmethyl-propyl) 1H pyrrolo[3,2-b]pyridine

{3 [3 6-Dimethyl 1-((S)-1-morpholin-4-ylmethyl propyl) 1H-pyrrolo[3 2 b]pyridin-5 yl]-6-isopropyl-pyridin 2 yl}-methyl-amine

5-(2 Ethyl-6-isopropyl-pyridin 3 yl)-3 6-dimethyl 1-((S)-1-morpholin-4 ylmethyl propyl)-1H pyrrolo[3,2 b]pyridine

1 [(S)-1-(3,3 Dimethyl-piperidin-1 ylmethyl)-propyl]-5-(2 methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

5-(2 Methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl 1-((S)-1-thiomorpholin-4-ylmethyl-propyl)-1H-pyrrolo[3,2 b]pyridine

1 [(S)-1-(4 4 Difl oro-piperid n-1 ylmethyl)-propyl] 5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyridine,

(R)-2 [5-(6 Isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] butan 1-ol

5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl 1-((R)-1 morpholin-4-ylmethyl propyl) 1H pyrrolo[3,2-b]pyridine,

5-(6-Isopropyl 2-methoxy pyridin 3 yl)-1-((R)-1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridine

{3 [3 6-Dimethyl 1-((R)-1 morpholin-4-ylmethyl propyl)-1H pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl} methyl-amine

5-(2 Ethyl-6 isopropyl pyridin 3 yl)-3 6-dimethyl 1-((R)-1 morpholin-4-ylmethyl-propyl)-1H-pyrrolo[3,2 b]pyridin

5-(2 Ethyl-6-isopropyl pyrid n 3 yl) 1-((R)-1 methoxymethyl propyl) 3 6-d methyl 1H pyrrolo[3 2 b]pyridine,

{6-Isopropyl 3 [1-((R) 1 methoxymethyl-propyl)-3 6-d methyl 1H pyrrolo[3 2 b]pyridin 5 yl] pyridin 2 yl} methyl-amine

5-(6-Isopropyl-pyridin 3 yl)-1-((R)-1 methoxymethyl-propyl)-3 6-d methyl 1H pyrrolo[3 2 b]pyrid ne

6 Ethyl 5-(6-isopropyl 2 methoxy-pyridin 3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2-b]pyrid ne

(S) 2 [6-Ethyl-5-(6 isopropyl 2 methoxy pyridin 3 yl) 3-methyl pyrrolo[3 2-b]pyridin 1 yl] propan 1-ol

6-Ethyl 5-(6 sopropyl pyridin-3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-3 methyl-1H pyrrolo[3 2-b]pyridi e

6-Ethyl 5-(2-ethyl-6 isopropyl pyridin 3 yl)-1-((S)-2 methoxy 1-methyl-ethyl) 3-methyl 1H-pyrrolo[3 2 b]pyridine

{3-[6 Ethyl 1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridin 5 yl] 6-isopropyl pyridin 2 yl} methyl-amine

(R)-1 [5-(6 Isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] buta 2-ol

1-[5-(6-Isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2 b]pyridin-1 yl] 2 methyl propan 2-ol

5-(6-Isopropyl 2-methoxy-pyridin 3 yl)-1-((R)-2-methoxy-butyl)-3 6-dimethyl-1H pyrrolo[3 2-b]pyridine

(R)-2 [6-Ethyl 5-(6-isopropyl 2-methoxy pyridin 3 yl)-3-methyl pyrrolo[3,2-b]pyridin 1 yl] propan-1-ol

(R)-2 [5-(2 Ethoxy-6-ethyl-5 methanesulfonyl-pyridin-3-yl)-6-ethyl 3-methyl-pyrrolo[3,2 b]pyridin-1 yl]-propan 1-ol

5-(2 Ethoxy-6-ethyl 5-methanesulfonyl-pyridin 3 yl)-6-ethyl 1-((R)-2 methoxy-1 methyl-ethyl)-3 methyl 1H-pyrrolo[3,2-b]pyridine

(R)-2 [6-Ethyl 5-(6-isopropyl-2-methoxy-pyridin 3 yl)-3 methyl pyrrolo[3,2-b]pyridin 1 yl]-butan 1-ol

(R)-2 [5-(2 Ethoxy-6-ethyl-5 methanesulfonyl pyridin 3 yl)-6-ethyl-3 methyl-pyrrolo[3,2-b]pyr din 1 yl] butan-1-ol

5-(2 Ethoxy-6-ethyl 5 methanesulfonyl pyridin 3 yl)-6-ethyl 1-((R)-1-methoxymethyl propyl) 3 methyl 1H pyrrolo[3 2 b]pyridine

6-Ethyl 5-(6-isopropyl 2-methoxy pyridin 3 yl)-1-((R)-1 methoxymethyl propyl)-3 methyl 1H-pyrrolo[3,2 b]pyridine

6-Ethyl 5-(6-isopropyl 2-methoxy-pyridin 3 yl)-1-((R)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyr dine

5-(2 Azetidin 1 yl-6-isopropyl-pyridin 3 yl)-1-((R)-1-methoxymethyl-propyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine

5-(2 Azetidin 1 yl-6-isopropyl pyridin 3 yl)-6-ethyl 1-((R)-1-methoxymethyl-propyl)-3 methyl 1H-pyrrolo[3,2 b]pyridine

{3-[6-Ethyl 1-((R)-1-methoxymethyl-propyl)-3-methyl 1H pyrrolo[3,2 b]pyridin-5 yl]-6-isopropyl pyridin 2 yl} methyl-amine

6 Ethyl 5-(2-ethyl-6 isopropyl-pyridin 3 yl)-1-((R)-1 methoxymethyl propyl)-3 methyl 1H-pyrrolo[3 2-b]pyridine

6-Ethyl 5-(2-ethyl-6-isopropyl-pyridin 3 yl)-1-((R)-2-methoxy-1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridine

{3-[6-Ethyl 1-((R)-2-methoxy-1 methyl-ethyl)-3 methyl-1H-pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl} methyl-amine

6-Ethyl 5-(4-isopropyl 2-methoxy phenyl)-1-((R)-2 methoxy-1 methyl-ethyl)-3-methyl 1H pyrrolo[3,2 b]pyridine

6-Ethyl 1-((R)-2 fluoro-1 methyl-ethyl)-5-(4-isopropyl 2 methoxy phenyl)-3 methyl 1H pyrrolo[3,2 b]pyridine

6-Ethyl 1-((R)-2 fluoro-1 methyl-ethyl)-5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 methyl 1H pyrrolo[3,2 b]pyridine

{5-Chloro-3 [7-chloro-6-ethyl 1-((R)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyrid n 5 yl]-6-isopropyl pyridin 2 yl} methyl-amine

{5-Chloro-3 [6-ethyl 1-((R)-2 methoxy 1 methyl-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyridin-5-yl]-6-isopropyl-pyridin 2 yl}-methyl-amine

{5 Bromo-3 [6-ethyl 1-((R)-2 methoxy 1-methyl-ethyl)-3 methyl-1H pyrrolo[3,2 b]pyridin-5 yl]-6-isopropyl pyrid 2 yl} methyl-amine

{5-Cyclopropyl-3 [6-ethyl 1-((R)-2-methoxy 1 methyl-ethyl)-3 methyl 1H-pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl-pyridin-2 yl} methyl amine

{5 Ethyl 3 [6-ethyl 1-((R)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-methyl-amine

(S)-2 [6 Bromo-5-(6- sopropyl 2 methoxy pyr din 3 yl)-3 methyl pyrrolo[3 2-b]pyrid n 1 yl] butan 1-ol

6-Bromo-5-(6-isopropyl 2 methoxy-pyridin-3 yl)-1-((S)-1 methoxymethyl propyl)-3 methyl 1H pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2 methoxy-pyridin-3 yl)-1-((S)-1-methoxymethyl-propyl)-3 methyl 1H pyrrolo[3,2 b]pyridin

5 Ethyl-6 [1-(1-ethyl propyl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridin-5 yl] 3 isopropyl 3H imidazo[4 5-b]pyridine

(3S,4R) 3-(2 Fluoro-ethoxy)-4-[5-(2-methoxy-4-trifluoromethoxy-phenyl)-3 6-dimethyl pyrrolo[3,2 b]pyridin 1 yl] pyrrolidine 1-carboxylic acid benzyl ester

(3S,4R) 3 (2 Fluoro-ethoxy)-4-[5-(2 methoxy-4 trifluoromethoxy phenyl)-3 6-dimethyl pyrrolo[3 2 b]pyrid n 1 yl] pyrrol dine-1-carboxylic acid methyl ester

(3S 4R)-3-(2 Fluoro-ethoxy)-4-[5-(6 sopropyl 2 methoxy pyrid n 3 yl)-3 6-dimethyl pyrrolo[3 2 b]pyridin 1 yl] pyrrolidine-1-carboxylic acid benzyl ester

(3S 4R)-3-(2 Fluoro-ethoxy)-4-[5-(6- sopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl pyrrolo[3 2 b]pyridin-1 yl] pyrrolidine-1-carboxylic ac d methyl ester

1 [(3R,4S)-4-(2 Fluoro-ethoxy)-1 methanesulfonyl pyrrolidin 3 yl] 5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-1H-pyrrolo[3,2-b]pyridine

1 [(3R,4S)-4-(2 Fluoro-ethoxy)-1 methyl pyrrolid n 3 yl] 5-(6 isopropyl 2 methoxy pyridin 3 yl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyridine

(3S 4R)-3-(2 Fluoro-ethoxy)-4-[5-(6-isopropyl 2 methoxy-pyridin 3 yl)-3 6-dimethyl-pyrrolo[3,2-b]pyridin 1 yl]-pyrrolidine-1-carboxylic acid 2 morpholin-4 yl-ethyl ester

3-Chloro-1 isopropyl-5-(6-isopropyl 2-methoxy-pyridin 3 yl)-6-methyl 1H pyrrolo[3 2 b]pyridine

3 Ethyl 5-(6-isopropyl 2-methoxy-pyridin 3 yl)-1-((S)-2-methoxy 1 methyl-ethyl)-6-methyl 1H-pyrrolo[3,2-b]pyridine

3-Chloro-1-((S)-2-methoxy 1 methyl-ethyl)-5-(2 methoxy-4 trifluoromethoxy-phenyl)-6-methyl 1H-pyrrolo[3,2 b]pyridine

3 Bromo-1-((S)-2-methoxy 1-methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2 b]py idine

1-((S)-2 Methoxy 1 methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2-b]pyridine

3 Fluoro-1-((S)-2-methoxy 1-methyl-ethyl)-5-(2 methoxy-4-trifluoromethoxy phenyl)-6-methyl 1H pyrrolo[3,2-b]pyridine

5-(6-Isopropyl 2 methoxy pyridin 3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-6-methyl 1H pyrrolo[3,2-b]pyridine

3-Chloro-5-(6-isopropyl-2 methoxy pyridin 3 yl)-1-((S)-2-methoxy-1 methyl-ethyl)-6-methyl 1H-pyrrolo[3,2 b]pyridine

(R)-2 [5-(6-Isopropyl 2 methoxy-pyridin-3 yl)-6-methyl pyrrolo[3 2-b]pyridin 1 yl]-butan 1-ol

3 Bromo-5-(6-isopropyl-2 methoxy-pyridin 3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-6-methyl 1H-pyrrolo[3,2-b]pyridine

(R)-2-[3-Chloro-5-(6-isopropyl-2 methoxy-pyridin 3 yl)-6-methyl pyrrolo[3 2-b]pyridin 1 yl]-butan-1-ol

5-(6-Isopropyl 2 methoxy pyridin-3 yl)-1-((R)-1-methoxymethyl propyl)-6-methyl-1H pyrrolo[3 2-b]pyridine

3-Chloro-5-(6-isopropyl 2 methoxy pyridin 3 yl)-1-((R)-1-methoxymethyl-propyl)-6-methyl 1H pyrrolo[3,2 b]pyridine

1 [1-((S)-2 Methoxy 1 methyl-ethyl)-5-(2-methoxy-4-trifluoromethoxy-phenyl)-6-methyl 1H pyrrolo[3,2 b]pyridin 7 yl]-pyrrolidine-2,5-dione

1 [5-(6 Isopropyl 2 methoxy-pyridin-3 yl)-1-((R)-1 methoxymethyl-propyl)-6-methyl-1H-pyrrolo[3,2 b]pyridin 7 yl]-pyrrolidine-2,5-dion

{3 [3-Chloro-1-((S)-2-methoxy 1 methyl-ethyl)-6 methyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6 isopropyl-pyridin 2 yl}-methyl-amine,

{3 [3-Chloro-1-((R)-1 methoxymethyl-propyl)-6 methyl 1H pyrrolo[3 2 b]pyridin 5 yl] 6-isopropyl pyridin 2 yl}-methyl-amine

3-Chloro-5-(2-ethyl 6-isopropyl pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-6-methyl 1H pyrrolo[3,2-b]pyridine

3-Chloro-5-(6-isopropyl pyrid n 3 yl)-1-((S) 2 methoxy-1-methyl-ethyl)-6-methyl 1H pyrrolo[3,2 b]pyridine

6-Ethyl 7 [1-((R)-1 hydroxymethyl-propyl) 3 6-dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl] 4-isopropyl 2 methyl-4H pyrido[2,3-b]pyrazin 3-one

6-Ethyl 2,4-d isopropyl 7 [1-((R)-1 meth xymethyl propyl)-3 6-d methyl 1H pyrrolo[3,2 b]pyridin 5 yl]-4H pyrido[2 3 b]pyraz n-3-one

2,6-Diethyl-4-isopropyl 7 [1-((R)-1 methoxymethyl propyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl]-4H pyrido[2 3 b]pyraz n-3-one

5-(6-Isopropyl 2-methoxy-pyridin-3 yl)-1-((S)-2 methoxy-1-methyl-ethyl)-6-methyl-1H pyrrolo[3 2 b]pyridine-3-carbonitril

5-(6 Isopropyl 2 methylamino-pyridin-3 yl) 1-((S) 2 methoxy 1 methyl-ethyl)-6 methyl 1H pyrrolo[3 2-b]pyridine-3-carbonitrile

6 Ethyl 7 [6-ethyl-1-((S)-2 methoxy 1-methyl-ethyl)-3-methyl 1H-pyrrolo[3,2-b]pyridin 5 yl]-4-isopropyl 2 methyl-4H pyrido[2 3-b]pyrazin 3-one

5-(2 Ethyl-6-methoxy pyridin 3 yl)-1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

5-(2 Ethyl-6-methoxy-pyridin 3 yl)-1-((S)-2 methoxy 1-methyl-ethyl) 3 6-dimethyl 1H pyrrolo[3 2-b]pyridine

5-(2 Ethyl-6-isopropoxy-pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridine

{6-Ethyl 5 [1-((S)-2-methoxy-1-methyl-ethyl)-3 6-dimethyl-1H-pyrrolo[3,2 b]pyridin 5 yl]-pyridin 2 yl}-dimethyl-amine,

5-(2 6-Diethyl pyridin 3 yl)-1-((S)-2 methoxy-1 methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine,

5-(2,6-Diethyl-pyridin-3-yl)-1-isopropyl-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

5-(2-Ethyl-6-isopropoxy-pyridin-3-yl)-1-isopropyl-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

[6-Ethyl-5-(1-isopropyl-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-5-yl)-pyridin-2-yl]-dimethyl-amine

5-(6-Cyclopropylmethoxy-2-ethyl-pyridin-3-yl)-1-((S)-2-methoxy-1-methyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

2-[5-(6-Isopropyl-2-methoxy-pyridin-3-yl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin-1-yl]-2-methyl-propan-1-ol

5-(6-Cyclopropyl-2-ethyl-pyridin-3-yl)-1-((S)-2-methoxy-1-methyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

5-(6-Ethoxy-2-ethyl-pyridin-3-yl)-1-((S)-2-methoxy-1-methyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

5-(6-Isopropyl-2-methoxy-pyridin-3-yl)-1-(2-methoxy-1,1-dimethyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

(R)-2-[5-(2-Ethyl-6-methoxy-pyridin-3-yl)-3,6-dimethyl-pyrrolo[3,2-b]pyridin-1-yl]-butan-1-ol

6-Ethyl-2-methoxy-5-[1-((S)-2-methoxy-1-methyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-5-yl]-N-methyl-nicotinamide

5-(2-Ethyl-6-methoxy-pyridin-3-yl)-1-((R)-1-methoxymethyl-propyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

1-{6-Ethyl-2-methoxy-5-[1-((S)-2-methoxy-1-methyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-5-yl]-pyridin-3-yl}-ethanone

5-(2-Ethyl-6-isopropyl-pyridin-3-yl)-1-(2-methoxy-1,1-dimethyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

{6-Isopropyl-3-[1-(2-methoxy-1,1-dimethyl-ethyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridin-5-yl]-pyridin-2-yl}-methyl-amine

5-(6-Ethoxy-2-ethyl-pyridin-3-yl)-1-((R)-1-methoxymethyl-propyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

5-(6-Cyclopropylmethoxy-2-ethyl-pyridin-3-yl)-1-((R)-1-methoxymethyl-propyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

5-(2-Ethyl-6-isopropoxy-pyridin-3-yl)-1-((R)-1-methoxymethyl-propyl)-3,6-dimethyl-1H-pyrrolo[3,2-b]pyridine

6-Ethyl 5-(2-ethyl-6-methoxy pyridin 3 yl)-1-((R)-2 fluoro-1-methoxymethyl-ethyl)-3 methyl 1H-pyrrolo[3 2 b]pyridine

5 [2-Ethyl-6-(2-methoxy-ethoxy)-pyridin 3 yl] 1-((S)-2-methoxy 1 methyl-ethyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2-methoxy-pyridin 3 yl)-1-((S)-2-methoxy 1-methyl-ethyl) 3 6,7 trimethyl 1H-pyrrolo[3 2 b]pyridin

{6-Isopropyl 3 [1-((S)-2 methoxy 1-methyl-ethyl)-3 6 7 trimethyl 1H pyrrolo[3,2 b]pyridin 5 yl] pyridi 2 yl} methyl-amine

5-(2 Ethyl-6 isopropyl-pyridin 3 yl)-1-((S)-2 methoxy 1 methyl-ethyl)-3 6 7-trimethyl-1H-pyrrolo[3 2-b]pyridine

{6 Isopropyl 3 [1-((S)-2 methoxy 1 methyl-ethyl)-3 6 7 trimethyl 1H-pyrrolo[3,2 b]pyridin 5 yl] pyridin 2 yl}-dimethyl-amine

5 (2 Azetid n-1 yl-6 isopropyl pyrid n-3 yl) 1-((S)-2 methoxy-1-methyl-ethyl)-3 6,7 trimethyl 1H pyrrolo[3 2 b]pyridine

[3-(3 6-Dimethyl 1-propyl 1H-pyrrol [3 2 b]pyrid n 5 yl)-6- sopropyl pyrid 2 yl]-(2 methoxy-ethyl)-amine

6 Isopropyl 3-(1 isopropyl-3 6-d methyl 1H pyrrolo[3 2-b]pyridin 5 yl) pyridin 2 yl]-(2 methoxy-ethyl)-amine

5-(6-Isopropyl 2 methoxy pyridin 3 yl) 1-((S)-2 methoxy 1 methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridine

{6-Isopropyl 3-[1-((S)-2 methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl] pyridin 2 yl}-dimethyl-amine

[6 Isopropyl 3-(1 isopropyl 3 6-dimethyl 1H-pyrrolo[3 2 b]pyrid n 5 yl)-pyridin 2 yl] dimethyl-amine

[3-(3 6-Dimethyl 1 propyl 1H-pyrrolo[3 2 b]pyridin 5 yl)-6-isopropyl pyridin 2 yl] dimethyl-amine

5-(2-Azetid n 1 yl-6-isopropyl pyridin 3 yl)-3 6-dimethyl 1-propyl 1H pyrrolo[3,2 b]pyrid e

5-(2 Azetidin 1 yl-6-isopropyl pyridin 3 yl)-1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

5-(2 Azetidin-1 yl-6 isopropyl-pyridin 3 yl)-1-((S)-2 methoxy-1 methyl-ethyl)-3 6 d methyl-1H pyrrolo[3,2 b]pyridine

5-[2-(3 3 Difluoro-azetidin-1 yl)-6-isopropyl-pyridin 3 yl] 1-((S)-2-methoxy-1 methyl ethyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine

5-(2 Ethoxy-6-isopropyl-pyridin-3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine

5-(2 Isopropoxy-6-isopropyl-pyridin-3 yl)-1-((S)-2 methoxy-1 methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridine

5-(6-Isopropyl 2-methyl-pyridin 3 yl)-1-((S)-2 methoxy-1-methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2-b]pyridin

[3-(3 6-Dimethyl 1-propyl-1H-pyrrolo[3,2 b]pyridin 5 yl)-6-isopropyl-pyridin 2 yl] isopropyl-amine

Isopropyl [6-isopropyl 3-(1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl)-pyridin-2 yl]-amine

{6-Isopropyl 3 [1-(2 methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2-b]pyridin 5 yl] pyridin 2 yl}-(2-methoxy-ethyl)-amine

Isopropyl {6-isopropyl-3 [1-((S)-2-methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl]-pyridin-2 yl}-amine

Ethyl {6-isopropyl 3-[1-((S)-2 methoxy 1, methyl-ethyl)-3 6-dimethyl-1H pyrrolo[3,2 b]pyridin-5 yl]-pyridin 2 yl}-amine,

1 Isopropyl 5 [6-isopropyl-2-(4 methyl-piperazin 1 yl)-pyridin-3 yl]-3 6-dimethyl 1H pyrrolo[3,2 b]pyridine

[5-Chloro-6-isopropyl 3-(1 isopropyl 3 6-dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl)-pyridin 2 yl]-ethyl-amine

1 Isopropyl 5-(6-isopropyl-2 methyl-pyridin 3 yl)-3 6-dimethyl 1H-pyrrolo[3,2 b]pyridine

5-(6-Isopropyl 2-methyl pyridin 3 yl)-3 6-dimethyl-1-propyl 1H pyrrolo[3,2 b]pyridine

1 Isopropyl 5-(6-isopropyl-pyridin-3 yl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridine

5-(6-Isopropyl 2-methoxy-pyridin-3 yl)-6-methoxy 1-((S)-2 methoxy-1 methyl-ethyl)-3 methyl 1H-pyrrolo[3,2-b]pyridine

Cyclopropyl {6-isopropyl-3 [1-((S)-2-methoxy 1-methyl-ethyl)-3 6-dimethyl 1H pyrrolo[3,2-b]pyridin 5 yl] pyridin-2 yl}-amine

5-(6-Isopropyl pyridin 3 yl)-6-methoxy 1-((S)-2-methoxy 1-methyl-ethyl)-3-methyl 1H pyrrolo[3,2-b]pyridine

5-(2-Ethyl-6-isopropyl-pyridin 3 yl)-6-methoxy-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridine

Ethyl {6-isopropyl 3 [6 methoxy 1-((S)-2-methoxy 1-methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridi 5 yl]-pyrid n 2 yl} amine

{6-Isopropyl 3 [6-methoxy 1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyridin 5 yl]-pyridin-2 yl}-dimethyl-amine

{6-Isopropyl-3-[6-methoxy 1-((S)-2 methoxy-1 methyl-ethyl)-3-methyl 1H-pyrrolo[3 2 b]pyridin 5 yl]-pyridin 2 yl} methyl-amine

6-Chloro-5-(6-isopropyl 2 methoxy pyridin 3 yl)-1-((S)-2-methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2-b]pyridine

6-Chloro-5-(2-ethyl-6-isopropyl-pyridin 3 yl)-1-((S) 2-methoxy-1 methyl-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyridine

6-Chloro-5-(6-isopropyl pyrid n-3 yl)-1-((S)-2 methoxy 1-methyl-ethyl)-3-methyl 1H pyrrolo[3,2 b]pyridine

{ [6-Chloro-1-((S) 2-methoxy 1 methyl-ethyl)-3-methyl 1H-pyrrol [3 2 b]pyridi 5 yl]-6 isopropyl pyridin 2 yl}-dimethyl-amine

{3 [6-Chloro-1-((S) 2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin-5 yl]-6 isopropyl-pyridin 2 yl}-methyl-amine

{3 [6-Chloro-1-((S)-2 methoxy 1 methyl-ethyl)-3 methyl 1H pyrrolo[3 2-b]pyridin 5 yl]-6 sopropyl-pyridin 2 yl}-ethyl-amine

{3 [6-Chloro-1-((R)-1 fluoromethyl-2-methoxy-ethyl)-3 methyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6- sopropyl pyridin 2 yl} methyl-amine

6-Chloro-5-(2-ethyl-6 isopropyl-pyridin-3 yl)-1-((R)-1 fluoromethyl-2-methoxy-ethyl)-3 methyl 1H-pyrrolo[3,2 b]pyridine

6-Chloro-1-((R)-1 fluoro-methyl 2 methoxy-ethyl)-5 (6 isopropyl 2 methyl pyridin 3 yl)-3 methyl 1H pyrrolo[3 2-b]pyridine

{5-Chloro-3 [1 ((R)-1 fluoromethyl 2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3,2 b]pyridin 5 yl]-6-isopropyl-pyridin-2 yl} methyl-amine

1-(R)-1 Fluoromethyl 2 methoxy-ethyl)-5-(6-isopropyl 2-methyl-pyrid n 3 yl)-3 6-dimethyl-1H pyrrolo[3 2 b]pyridine

Ethyl {3 [1-((R)-1 fluoromethyl 2 methoxy-ethyl)-3 6-dimethyl 1H pyrrolo[3 2 b]pyridin 5 yl]-6-isopropyl pyridin 2 yl}-amine

2 Bromo-7-(1-ethyl-propyl)-3-(2 methoxy-4-trifluoromethoxy phenyl)-5-methyl 5H pyrrolo[2,3-b]pyrazine

7-(1 Ethyl propyl)-3-(2-methoxy-4-trifluoromethoxy phenyl)-5 methyl 5H-pyrrolo[2 3 b]pyrazine

2 Ethyl 7-(1-ethyl-propyl)-3-(2 methoxy-4-trifluoromethoxy phenyl)-5-methyl 5H pyrrolo[2 3-b]pyrazine

7-(1 Ethyl propyl)-3-(2 methoxy-4-trifluoromethoxy-phenyl)-2 5-dimethyl 5H pyrrolo[2,3 b]pyrazine

2 Ethyl-7-(1-ethyl-propyl)-3-(6-isopropyl-2-methoxy-pyridin 3 yl)-5-methyl-5H pyrrolo[2,3-b]pyrazine

2 Ethyl 3-(2-ethyl-6-isopropyl-pyridin-3 yl)-7-(1-ethyl propyl)-5-methyl 5H-pyrrolo[2,3 b]pyrazine

{3-[2 Ethyl 7-(1-ethyl-propyl)-5-methyl-5H pyrrolo[2 3 b]pyrazin-3 yl]-6-isopropyl pyridin 2 yl}-methyl-amine

Diethyl {4-ethyl-5 [2-ethyl 7-(1-ethyl propyl)-5 methyl 5H-pyrrolo[2,3 b]pyrazin-3 yl]-pyridin 2 yl}-amine

2 Ethyl 7-(1-ethyl-propyl)-3-(3 isopropyl 5 m thoxy 2 3-dihydro-furo[3 2 b]pyr din-6-yl)-5-methyl 5H pyrrolo[2 3 b]pyrazine

2-[3-(2-Methoxy-4-trifluoromethoxy-phenyl)-2,5-dimethyl-5H pyrrolo[2,3 b]pyrazin-7 yl]-propan 1-ol

7-(2 Methoxy 1 methyl-ethyl)-3-(2-methoxy-4-trifluoromethoxy phenyl)-2 5-dimethyl-5H-pyrrolo[2,3 b]pyrazine

2 [3-(2 Methoxy-4-trifluoromethoxy phenyl)-2 5-dimethyl 5H pyrrolo[2 3-b]pyrazin-7 yl]-propionic acid methyl ester

2-[3-(6-Isopropyl 2 methoxy-pyridin 3 yl)-2 5-dimethyl 5H-pyrrolo[2 3-b]pyrazin-7 yl]-propan 1-ol

Methanesulfonic acid 2-[3-(6-isopropyl 2 methoxy pyridin 3 yl)-2 5-dimethyl 5H pyrrolo[2 3-b]pyrazin 7 yl]-propyl ester

3-(6-Isopropyl 2 methoxy-pyridin-3 yl)-7-(2-methoxy 1-methyl-ethyl)-2 5-dimethyl 5H pyrrolo[2,3-b]pyrazine

3-(6-Isopropyl-2 methoxy-pyridin-3 yl)-2 5-dimethyl 7-(1 methyl 2 morpholin-4-yl-ethyl)-5H pyrrolo[2 3-b]pyrazine

7-sec-Butyl-3-(6-isopropyl 2-methoxy pyridin 3 yl)-2,5-dimethyl 5H pyrrolo[2,3 b]pyrazine

7 Isopropyl 3-(6-isopropyl-2-methoxy pyridin-3 yl)-2,5-dimethyl 5H pyrrolo[2 3 b]pyrazine

2 [3-(6-Isopropyl-2 methoxy-pyridin 3 yl)-2,5-dimethyl 5H pyrrolo[2,3 b]pyrazin-7 yl] butan 1-ol

3-(6-Isopropyl 2 methoxy pyridin 3 yl)-7-(1 methoxymethyl propyl)-2,5-dimethyl 5H pyrrolo[2,3 b]pyrazi e

Methanesulfonic acid 2-[3 (6-isopropyl 2 methoxy pyridin 3 yl)-2,5-dimethyl 5H pyrrolo[2 3 b]pyrazin 7-yl] butyl ester

2 Ethyl 7 isopropyl 3-(6-isopropyl 2-methoxy-pyridin 3 yl)-5 methyl 5H pyrrolo[2,3 b]pyrazine

3-(2 Ethyl-6-isopropyl-pyridin 3 yl)-7-(2 methoxy 1-methyl-ethyl)-2 5-dimethyl 5H pyrrolo[2,3-b]pyrazine

2 Ethyl 3-(2-ethyl-6 sopropyl pyr di 3 yl)-7 isopropyl 5 methyl 5H-pyrrolo[2,3 b]pyrazine

[3-(2 Ethyl 7 isopropyl-5 methyl 5H-pyrrolo[2 3 b]pyrazin 3 yl)-6 isopropyl pyridin 2 yl]-methyl amine

{6-Isopropyl-3 [7-(2 methoxy 1 methyl-ethyl) 2 5-dimethyl 5H pyrrolo[2,3 b]pyrazin 3 yl] pyridin 2 yl}-methyl-amine

{4 Ethyl 5 [2-ethyl 7-(1-ethyl-propyl)-5-methyl 5H pyrrolo[2,3 b]pyraz n 3 yl] pyridin-2 yl}-dimethyl-amine

Ethyl {4-ethyl 5 [2-ethyl 7-(1-ethyl-propyl)-5-methyl-5H-pyrrolo[2,3-b]pyrazin-3 yl] pyridin 2 yl} methyl-amine,

2 2 Diethyl 7 7' bis-(1-ethyl-propyl)-5 5 -dimethyl 5H 5'H [3,3']b [pyrrolo[2,3 b]pyrazinyl]

5 Ethyl-6-[2-ethyl 7 (1-ethyl-propyl)-5 methyl 5H pyrrolo[2 3 b]pyrazin 3 yl] 3 isopropyl 3H imidazo[4 5 b]pyridine

2 Ethyl 7-(2-methoxy-ethyl)-3-(2 methoxy-4 trifluoromethoxy phenyl)-5 methyl-5H pyrrolo[2 3 b]pyrazine

3 [2 Ethyl 3-(2 methoxy-4-trifluoromethoxy phenyl)-5 methyl 5H pyrrolo[2 3 b]pyrazin 7 yl]-propionitrile

5-Bromo-3-(1-ethyl propyl)-6-(2-methoxy-4-trifluoromethoxy-phenyl)-1 methyl 1H pyrrolo[2 3-b]pyridine

3-(1 Ethyl-propyl)-6-(? methoxy-4-trifluoromethoxy-phenyl)-1 5-dimethyl 1H pyrrolo[2,3-b]pyridine

5-Chloro-3-(1-ethyl propyl)-6-(2 methoxy-4-trifluoromethoxy-phenyl)-1-methyl-1H pyrrolo[2 3 b]pyridine

3-(1 Ethyl propyl)-6-(2 methoxy-4-trifluoromethoxy-phenyl)-1 5-dimethyl 1H pyrrolo[2 3 b]pyridine

3-sec Butyl-6-(6-isopropyl 2-methoxy pyridin 3 yl)-1 5-dimethyl 1H-pyrrolo[2 3 b]pyridine

3-sec-Butyl-6-(2-ethyl-6-isopropyl-pyridin-3 yl)-1 5-dimethyl-1H pyrrolo[2,3 b]pyridine

[3-(3-sec-Butyl 1 5-dimethyl 1H-pyrrolo[2 3-b]pyridin-6 yl)-6-isopropyl pyridin-2 yl] methyl-amine

2 [6-(6 Isopropyl 2-methoxy pyridin 3 yl)-1 5-dimethyl 1H pyrrolo[2 3-b]pyridin 3 yl] butan 1-ol

6-(6-Isopropyl 2 methoxy-pyridin-3 yl)-3-(1 methoxymethyl-propyl)-1 5-dimethyl 1H pyrrolo[2 3 b]pyridine

5 Bromo-3 isopropyl-6-(6-isopropyl 2-methoxy-pyridin 3 yl)-1 methyl 1H-pyrrolo[2 3 b]pyrid ne

3 Isopropyl-6-(6- sopropyl 2 methoxy pyridin 3 yl)-1 5-dimethyl 1H-pyrrolo[2 3 b]pyridine

3 (1 Ethoxymethyl propyl)-6-(6-isopropyl 2 methoxy pyridin-3 yl)-1 5-dimethyl 1H pyrrolo[2 3-b]pyridine and

5 Ethyl-3 isopropyl-6-(6 isopropyl 2 methoxy-pyridin 3 yl)-1-methyl 1H-pyrrolo[2 3 b]pyridine

42 A compound or salt according to any of Claims 1-41 wherein, in a standard in vitro CRF receptor binding assay the compound exhibits an IC_{50} value for CRF receptors of less than or equal to 1 micromolar

43 A compound or salt according to any of Claims 1-41 wherein, in a standard in vitro CRF receptor binding assay the compound exhibits an IC_{50} value for CRF receptors of less than or equal to 100 nanomolar

44 A compound or salt according to any of Claims 1-41 wherein in a standard in vitro CRF receptor binding assay the compound exhibits an IC_{50} value for CRF receptors of less than or equal to 10 nanomolar

45 A method for treating an anxiety disorder a stress-related disorder or an eating disorder comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or salt according to any of Claims 1-41

46 A method for treating depression or bipolar disorder comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or salt according to any of Claims 1-41

47 A method for treating anorexia nervosa, bulimia nervosa, or obesity comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound or salt according to any of Claims 1-41

48 A compound or salt according to any of Claims 1-41 wherein in a standard in vitro Na channel functional assay the compound does not show any statistically significant detectable Na channel modulatory activity at the $p < 0.05$ level of significance in a standard parametric test of statistical significance

49 A method for demonstrating the presence of CRF receptors in cell or tissue samples, said method comprising

preparing a plurality of matched cell or tissue samples,

preparing at least one control sample by contacting (under conditions that permit binding of CRF to CRF receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously been contacted with any compound or salt of any of Claims 1-41) with a control solution comprising a detectably labeled preparation of a selected compound or salt of any of Claims 1-41 at a first measured molar concentration said control solution further comprising an unlabelled preparation of the selected compound or salt at a second measured molar concentration, which second measured concentration is greater than said first measured concentration,

preparing at least one experimental sample by contacting (under conditions that permit binding of CRF to CRF receptors within cell and tissue samples) at least one of the matched cell or tissue samples (that has not previously been contacted with any compound or salt of any of Claims 1-41) with an experimental solution comprising the detectably labeled preparation of the selected compound or salt at the first measured molar concentration, said experimental solution not further comprising an unlabelled preparation of any compound or salt of any of Claims 1-41 at a concentration greater than or equal to said first measured concentration

washing the at least one control sample to remove unbound selected compound or salt to produce at least one washed control sample

washing the at least one experimental sample to remove unbound selected compound or salt to produce at least one washed experimental sample

measuring the amount of detectable label of any remaining bound detectably labeled selected compound or salt in the at least one washed control sample

measuring the amount detectable label of any remaining bound detectably labeled selected compound or salt in the at least one washed experimental sample

comparing the amount of detectable label measured in each of the at least one washed experimental sample to the amount of detectable label measured in each of the at least one washed control sample

wherein, a comparison that indicates the detection of a greater amount of detectable label in the at least one washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of CRF receptors in that experimental sample

50 A method of inhibiting the binding of CRF to a CRF1 Receptor which method comprises

contacting a solution comprising CRF and a compound or salt of any of Claims 1 to 41 with cell expressing the CRF receptor wherein the compound or salt is present in the solution at a concentration sufficient to inhibit *v tro* CRF binding to IMR32 cells

51 The method of Claim 50 wherein the cell expressing the CRF receptor is a neuronal cell that is contacted in vivo in an animal and wherein the solution is a body fluid of said animal

52. The method of Claim 51 wherein the animal is a human patient

53 A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or salt of any of Claims 1-41

54 A package comprising a pharmaceutical composition of claim 53 in a container and further comprising indicia comprising at least on of

instructions for using the composition to treat a patient suffering from an anxiety disorder or

instructions for using the composition to treat a pat ent suffering from a stress-related disorder or

instructions for using the composition to treat a patient suffering from an eating disorder

55 A package comprising a pharmaceutical composition of laim 53 in a container and furthe comprising i dicia comprising at least one of instructions fo usi g the composition to treat a patient suffering from depression o instructions for using the composition to treat a patient suffering from a bipola disorder

PIRIDINAS, PIRAZINAS Y PIRIMIDINAS FUSIONADAS CON HETEROARILO COMO LIGANDOS RECEPTORES CRF1

Está solicitud reivindica prioridad de la solicitud provisional U S serie No 60/500 414 presentada en septiembre 5 2003

CAMPO DE LA INVENCIÓN

La presente invención se relaciona con compuestos de pirdina pirazina y pirimidina fusionados a heteroarilos sustituidos novedosos que se unen con alta selectividad y/o la afinidad a receptores CRF (Receptores del Factor de Liberación de Corticotropina) Esta invención también se relaciona con composiciones farmacéuticas que comprenden tales compuestos y con el uso de tales compuestos en el tratamiento de de desórdenes siquiátricos y enfermedades neurológicas que incluyen depresión fuerte desórdenes relacionados con la ansiedad desórdenes por tensión post traumática parálisis supranuclear y desórdenes de la alimentación así como también tratamiento por desórdenes inmunológicos cardiovasculares o relacionados con el corazón e hipersensibilidad colónica asociada con disturbios psicopatológicos y tensión Adicionalmente esta invención se relaciona con el uso de tales compuestos como sondas para la localización de receptores CRF en células y tejidos Los receptores CRF preferidos son los receptores CRF1

ANTECEDENTES DE LA INVENCIÓN

El factor de liberación de corticotropina (CRF) un péptido de 41 aminoácidos es el regulador psicológico primario de la secreción de péptido derivada de

proopiomelanocortina (POMC) de la glándula pituitaria anterior Además de su papel endocrino en la glándula pituitaria la localización inmunohistoquímica del CRF ha demostrado que la hormona tiene una amplia distribución extra hipotalámica en el sistema nervioso central y produce un amplio espectro de efectos autonómicos electrofisiológicos y de comportamiento consistentes con un papel de neurotransmisor o neuromodulador en el cerebro También existe evidencia de que el CRF juega un papel significativo en integrar la reapuesta del sistema inmune a estresantes fisiológicos psicológicos e inmunológicos

Los datos clínicos suministran evidencia de que el CRF tiene un papel en los desórdenes siquiátricos y las enfermedades neurológicas que incluyen depresión desórdenes relacionados con la ansiedad y desórdenes de la alimentación Un papel del CRF también ha sido postulado en la etiología y patofisiología de la enfermedad de Alzheimer a enfermedad de Parkinson la enfermedad de Huntington la parálisis supranuclear progresiva y la esclerosis lateral amiotrófica en la medida que ellos se relacionan con la disfunción de neuronas CRF en el sistema nervioso central

En el desorden afectivo o la depresión fuerte la concentración de CRF se incrementa significativamente en el fluido espinal del cerebro (CSF) de los individuos libres de droga Adicionalmente la densidad de los receptores CRF se disminuye significativamente en la corteza frontal de las victimas de suicidio consistente con una hipersecreción de CRF Además existe una adrenocorticotropina truncada (ACTH) que responde al CRF (administrada i v) observada en pacientes deprimidos Los estudios preclínicos en ratas y en primates no humanos suministran soporte adicional para la hipótesis de que la hipersecreción de CRF puede estar involucrada en los síntomas vistos en la

depresión humana También existe evidencia preliminar que los antidepresivos tricíclicos pueden alterar niveles de CRF y así modular los numeros de los receptores CRF en el cerebro

El CRF también ha estado implicado en la etiología de desórdenes relacionados con la ansiedad El CRF produce efectos ansiogénicos en animales e interacciones entre ansiolíticos de benzodiazepina/no benzodiazepina y el CRF ha demostrado una amplia variedad de modelos de ansiedad de comportamiento Los estudios preliminares que utilizan el CRF ovino α helicoidal antagonista de receptor CRF putativo (9-41) en una amplia variedad de paradigmas de comportamiento demuestran que el antagonista produce efectos similares a ansiolíticos que son cualitativamente similares a los de benzodiazepinas Estudios que unen los neuroquímicos endocrinos y receptores han demostrado todas las interacciones entre CRF y anciolíticos de benzodiazepina que suministran evidencia adicional del involucramiento de CRF en estos desórdenes El clordiazepóxido atenua los efectos ansiogénicos del CRF tanto en ensayos de conflicto como en ensayos de alarma acústica en ratas El antagonista receptor de benzodiazepina Ro 15-1788 que estaba solo sin actividad de comportamiento en los ensayos de conflicto operantes reversa los efectos del CRF de una manera dependiente de dosis aunque el agonista inverso de benzodiazepina FG 7142 mejora las acciones del CRF

El CRF ha estado implicado en al patogénesis de ciertas enfermedades inmunológicas cardiovasculares o relacionadas con el corazón tal como la hipertensión taquicardia y falla cardiaca congestiva apoplejía y osteoporosis así como también en nacimientos prematuros enanismo sicosocial fiebre inducida

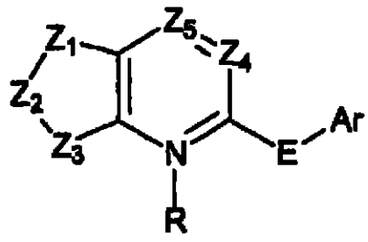
por tensión ulcera diarrea íleo post operativo e hipersensibilidad colónica asociada con disturbios y tensión psicopatológica

Los mecanismos y sitios de acción a través de los cuales los ansiolíticos y los antidepresivos convencionales producen sus efectos terapéuticos permanecen para ser completamente elucidados Se han hecho hipótesis sin embargo de que ellos están involucrados en la supresión de la hipersecreción CRF que se observa en estos desórdenes De particular interés son los estudios preliminares que examinan los efectos de un péptido antagonista receptor de CRF (CRF_{9-41} α helicoidal) en una variedad de paradigmas de comportamiento ha demostrado que los antagonistas CRF producen efectos similares a ansiolíticos cualitativamente similares a los de las benzodiazepinas

RESUMEN DE LA INVENCIÓN

La invención suministra compuestos novedosos de Fórmula I (mostrados adelante) y composiciones farmacéuticas que comprenden los compuestos de Fórmula I y al menos un portador excipiente farmacéuticamente aceptable Tales compuestos se unen a los receptores de superficie celular preferiblemente los receptores de proteína acoplados con G especialmente los receptores CRF (que incluyen los receptores CRF1 y CRF2) y más preferiblemente los receptores CRF 1 Los compuestos precedidos de la invención exhiben alta afinidad por los receptores CRF preferiblemente los receptores CRF 1 Adicionalmente los compuestos preferidos de la invención también exhiben alta especificidad por receptores CRF (es decir que exhiben alta selectividad comparados con su unión a receptores no CRF) Preferiblemente ellos exhiben alta especificidad por receptores CRF 1

Así en ciertos aspectos la invención suministra compuestos de Fórmula I-a



I-a

y las sales farmacéuticamente aceptables de estos en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1-C_4

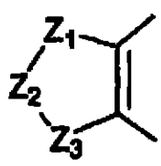
m es 0 1 o 2

Ar se escoge de

fenilo que es mono- di o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido y heteroarilo opcionalmente mono- di- o tri-sustituido dicho heteroarilo tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a 3 heteroátomos seleccionado del grupo que consiste de N O y S

R es oxígeno o está ausente

el grupo



representa un sistema de anillo de 5 miembros saturado insaturado o aromático que contiene 0 o 1 heteroátomos en donde

Z_1 es CR_1 o CR_1R_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 o CR_3R_3

R_1 se escoge de hidrógeno halógeno hidroxi ciano amino alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido alcoxi opcionalmente sustituido mono o dialquilamino opcionalmente sustituido cicloalquilo opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido alquiltio opcionalmente sustituido alquilsulfinilo opcionalmente sustituido alquilsulfonilo opcionalmente sustituido mono-o dialquilcarboxamida opcionalmente sustituida anilo carbocíclico opcionalmente sustituido heterociclo opcionalmente sustituido y heteroarilo opcionalmente sustituido dicho heterociclo o heteroarilo opcionalmente sustituido tienen de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionado del grupo que consiste de N O y S

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo haloalquilo alcoxi aminoalquilo hidroxialquilo y mono y dialquilamino en donde cuando R_1 o R_1 es alquilo opcionalmente sustituido entonces R_3 es alquilo C_{1-3} opcionalmente sustituido

R_1 R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo haloalquilo y aminoalquilo

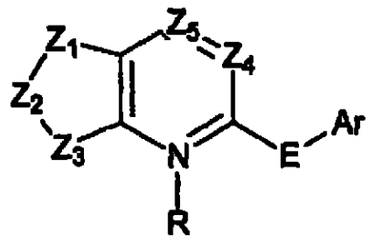
R_2 se escoge de hidrógeno alquilo opcionalmente sustituido alquilo opcionalmente sustituido y aminoalquilo opcionalmente sustituido

Z_4 es NR o CR_4

Z_5 es NR o CR_5

R_4 y R_5 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido alcoxi opcionalmente sustituido mono o dialquilamino opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido alquiltio opcionalmente sustituido alquilsulfinilo opcionalmente sustituido alquilsulfonilo opcionalmente sustituido mono-o dialquilcarboxamida opcionalmente sustituida anilo carbocíclico opcionalmente sustituido y heteroanilo opcionalmente sustituido dicho heteroanilo opcionalmente sustituido tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a cerca de 3 heteroátomos seleccionados del grupo que consiste de N O y S

En ciertos otros aspectos la invención suministra los compuestos de Fórmula I-b



Fórmula I b

o una sal farmacéuticamente aceptable de estos en donde

E es un enlace simple O $S(O)_m$ NR NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1 C_4

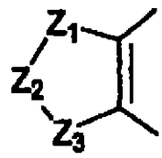
m es 0 1 o 2

R es oxígeno o está ausente

Ar se escoge de

fenilo que es mono- di o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido y opcionalmente heteroarilo mono- di o tri sustituido dicho heteroarilo tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionado del grupo que consiste de N O y S

el grupo



representa un sistema de anillo saturado insaturado o aromático que comprende 0 o 1 heteroátomos en donde

Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es CR_2 o CR_2R_2

Z_3 es CR_3 CR_3R_3 o NR_3

R_1 y R_1 son escogidos de hidrógeno alquiloC_1 C_{10} alquenilo C_2-C_{10} alquinilo C_2-C_{10} cicloalquilo C_3 C_7 (benzo) cicloalquilo C_3-C_7 (cicloalquil C_3 C_7) alquilo C_1 C_4 heterocicloalquilo C_{3-9} (heterocicloalquilo C_{3-9}) alquilo C_1-C_4 (benzo) heterocicloalquilo C_{3-9} ((benzo) heterocicloalquilo C_{3-9}) alquilo C_1 C_4 y halo (C_1 C_6) alquilo cada uno de los cuales es sustituido con 0 o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1 C_6 alcoxi C_1 C_6 halo alcoxi C_1-C_6 alcanoilo C_1 C_6 alcanoiloxi C_1-C_6 alcoxicarbonilo C_1-C_6 N (alcanoilo C_1 C_6) N (alquil C_0-C_6) amino N (alcanoiloxi

C_1-C_8) N (alquil C_0-C_8) amino N-(alcoxicarbonilo C_1-C_8) N (alquil C_0-C_8) amino alquilsulfonamida C_1-C_6 alquilsulfonilo C_1-C_8 alquilsulfoniloxi C_1-C_8 hidroxialquilo C_1-C_8 alcoxi C-C_8 alquilo C_1-C_8 haloalcoxi C_1 C_8 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono-y di (C_1 C_8) alquilamino N (alcanoilo C_1-C_8) N (alquil C_0-C_8) amino N (alcanoiloxi C_1 C_8) N (alquil C_0-C_8) amino N (alcoxicarbonilo C_1 C_8) N (alquil C_0-C_8) amino mono-y di (C_1 C_8) alquilcarbamoilo XR_C y X Z con la condición que R_1 y R_1 no sea alquilo sustituido con arilo o heteroarilo

R_2 se escoge de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1 C_3 halo (C_1 C_3) alquilo alcoxi C_1 C_3 amino (C_1 C_3) alquilo y mono y di (C_1 C_8) alquilamino

R_3 se escoge de hidrógeno hidroxi amino halógeno ciano nitro alquilo C_1 C_3 halo (C_1-C_3) alquilo alcoxi C_1 C_3 amino (C_1 C_3) alquilo hidroxi (C_1-C_3) alquilo ciano (C_1-C_3) alquilo y mono y di (C_1 C_3) alquilamino

R_3 se escoge de hidrógeno hidroxi amino alquilo C_1-C_3 halo (C_1 C_3) alquilo alcoxi C_1-C_3 amino (C_1 C_3) alquilo hidroxi (C_1 C_3) alquilo ciano (C_1-C_3) alquilo y mono y di (C_1-C_3) alquilamino

R_1 R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1 C_8 halo (C_1 C_8) alquilo y amino (C_1 C_8) alquilo

Z_4 es NR o CR_4

Z_5 es NR o CR_5

R_4 y R_5 son independientemente escogidos de hidrógeno halógeno ciano nitro amino mono o di (carbhidrilo C_1-C_6)amino carbhidrilo C_1 C_6 (ciclocarbhidrilo C_3-C_7) carbhidrilo C_0-C_4 -O(ciclocarbhidrilo C_3 C_7) halo (C_1 C_6) carbhidrilo -O(halo (C_1-C_6) carbhidrilo) -O(carbhidrilo C_1 C_6) S(O)n(carbhidrilo C_1-C_6) y heterocicloalquilo de 4 a 7 miembros

donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con una o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono y di (C_1-C_4) alquilamino

y

donde cada carbhidrilo C_3-C_7 heterocicloalquilo es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1 C_4 y mono y di (C_1-C_4) alquilamino o

R_5 tomado en combinación con R_1 o R_1 forman un heterociclo de 5 a 9 miembros

R_A es independientemente seleccionado en cada ocurrencia de halógeno ciano nitro halo (C_1 C_6) alquilo halo (C_1 C_6) alcoxi hidroxi amino alquilo C_1 C_6 sustituido con 0 2 R_B alquenilo C_2-C_6 sustituido con 0-2 R_B alquinilo C_2-C_6 sustituido con 0 2 R_B cicloalquiloC$_3$ C_7 sustituido con 0-2 R_B (cicloalquil C_3 C_7) alquilo C_1-C_4 sustituido con 0 2 R_B alcoxi C_1-C_6 sustituido con 0-2 R_B NH (alquilo C_1-C_6) sustituido con 0 2 R_B N(alquilo C_1-C_6) (alquilo C_1 C_6) cada alquilo C_1 C_6 independientemente sustituido con 0 2 R_B XR_C y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1 C_4 O(alquilo C_1 C_4) NH (alquilo C_1 C_4) N(alquilo C_1 C_4)(alquil C_1-C_4) S(O)n(alquilo) halo (C_1 C_4) alquilo halo (C_1 C_4) alcoxi CO(alquilo C_1 C_4l) CONH (alquilo C_1 C_4) CON(alquilo C_1-C_4) (alquilo C_1-C_4) XR_C y Y

R_C y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia de

hidrógeno y

grupos alquilo rectos ramificados o cíclicos que incluyen grupos (cicloalquil) alquil que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contiene cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituidos con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1 C_6 NH (alquilo C_1 C_6) N(alquilo C_1 C_6)(alquilo C_1 C_6) NHC(=O)(alquilo C_1-C_6) N(alquilo C_1-C_6)C(=O)(alquilo C_1 C_6) NHS(O) (alquilo C_1-C_6) -S(O) (alquilo C_1 C_6) S(O) NH(alquilo C_1 C_6) S(O) N(alquilo C_1 C_6)(alquilo C_1 C_6) y Z

X es independientemente seleccionado en cada ocurrencia del grupo que consiste de -O- C(=O)O- $S(O)_n$- NH NR_D- C(=O)NH -C(=O)NR_D- -S(O) NH S(O) NR_D- OC(=S)S NHC(=O) NR_DC(=O) NHS(O) $OSiH_2$- OSiH(alquilo C_1-C_4) OSi(alquilo C_1-C_4)(alquilo C_1 C_4) y NR_DS(O)$_n$-

Y y Z son independientemente seleccionados en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituidos con uno o más

sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino ciano alquilo C_1 C_4 O(alquilo C_1 C_4) NH(alquilo C_1 C_4) N(alquilo C_1 C_4)(alquilo C_1-C_4) C(O)(alquilo C_1 C_4) y S(O) (alquilo) en donde dichos grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S el punto de unión es cualquier carbono o nitrógeno y

n es independientemente seleccionado en cada ocurrencia de 0 1 y 2

Ciertos compuestos preferidos de la Fórmula I-a o la Fórmula I b incluyen aquellos en los cuales al menos uno de Z_4 y Z_5 no es NR Ciertos otros compuestos preferidos de Fórmula I-a o Fórmula I b incluyen aquello en los cuales Z_4 se selecciona de N y CR_4 y Z_5 se selecciona de N y CR_5

Ciertos compuestos preferidos de la Fórmula I-b incluyen aquellos compuestos en los cuales

Ar se escoge de fenilo el cual es mono di o tri-sustituido con R_A y 1 naftilo 2 naftilo pindilo pirimidinilo pirazinilo pindizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono- di- o tri sustituido con R_A y

R_1 y R_1 son escogidos de alquilo C_1-C_{10} alquenilo C_2-C_{10} alquinilo C_2-C_{10} cicloalquilo C_3 C_7 (cicloalquilo C_3-C_7) alquilo C_1 C_4 (benzo) cicloalquilo C_3 C_7 (benzo) heterocicloalquiloC_{3-9}

((benzo) heterocicloalquil C_{3-9})alquilo C_1 C_4 y halo (C_1-C_6) alquilo cada uno de los cuales es sustituido con 0 1 2 o 3 sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1-C_6 o alcoxi C_1-C_6 halo C_1-C_6 alcoxi alcanoilo C_1 C_6 alcanoiloxi C_1 C_6 alcoxicarbonilo C_1 C_6 N (alcanoilo C_1 C_6) N (alquil C_0-C_6)amino N (alcanoiloxi C_1 C_6) N (alquil C_0-C_6)amino N (alcoxicarbonilo C_1-C_6) N-(alquil C_0-C_6)amino alquilo sulfonamida C_1-C_6 alquilosulfonilo C_1 C_6 alquilosulfoniloxi C_1-C_6 hidroxialquilo C_1-C_6 alcoxi C_1-C_6 alquilo C_1 C_6 haloalcoxi C_1 C_6 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono- y di (C_1-C_6) alquilamino N (alcanoilo C_1 C_6) N (alquil C_0-C_6)amino N (alcanoiloxi C_1-C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1 C_6) N (alquil C_0-C_6)amino mono- y di (C_1 C_6) alquilcarbamoilo XR_C y X Z

Como se usa aquí el término Fórmula I está destinado generalmente a referirse a compuestos de la Fórmula I-a o la Fórmula I b y las sub fórmulas de estos

La invención comprende además métodos para tratar pacientes que sufren de ciertos desórdenes con una cantidad terapéuticamente efectiva de al menos un compuesto de la invención Estos desórdenes incluyen desórdenes CNS desórdenes particularmente afectivos desórdenes de ansiedad desórdenes relacionados con la tensión desórdenes de alimentación y abuso de sustancias El paciente que sufre de estos desórdenes puede ser un humano u otro animal (preferiblemente un mamífero) tal como un animal de compañía domesticado (mascota) o animal de rebaño Los compuestos preferidos de la invención para tales propósitos terapéuticos son aquellos que antagonizan la unión del CRF a receptores CRF (preferiblemente CRF1 o menos preferiblemente receptores CRF2) La capacidad de los compuestos para actuar como antagonistas se puede medir como un valor IC_{50} como se describe adelante

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De acuerdo aún con otro aspecto la presente invención suministra composiciones farmacéuticas que comprenden compuestos de fórmula I o sales farmacéuticamente aceptables (por cuyo término también está comprendido solvatos farmacéuticamente aceptables) de estos cuyas composiciones son utiles para el tratamiento de los desórdenes anteriormente citados La invención además suministra métodos para tratar pacientes que sufren de cualquiera de los desórdenes anteriormente citados con una cantidad efectiva de un compuesto o composición de la invención

Adicionalmente esta invención se relaciona con el uso de los compuestos de la invención (particularmente compuestos marcados de esta invención) como sondas para la localización de receptores en células y tejidos y como estándares y reactivos para uso para determinar las características de unión a receptor de los compuestos de ensayo

Los compuestos de pirdina pirazina y pirimidina fusionado con heteroarilo prefendos de la invención exhiben buena actividad es decir una concentración inhibitoria máxima media IC_{50} de menos de 1 milimolar en un ensayo de unión de receptor CRF in vitro estándar tal como el ensayo suministrado en el Ejemplo 51 que sigue Los compuestos de pirdina pirazina y pirimidina fusionados con heteroarilo sustituidos particularmente preferidos de la invención exhiben IC_{50} de aproximadamente 1 micromolar menos aun más preferiblemente un IC_{50} de aproximadamente 100 nanomolar o menos aun más preferiblemente un IC_{50} de aproximadamente 10 nanomolar o menos Ciertos compuestos particularmente prefendos de la invención exhibirán un IC_{50} de 1 nanomolar o menos en tal ensayo de unión de receptor CRF in vitro estándar definido

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

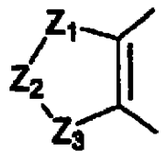
Además de los compuestos de Fórmula I-a descritos anteriormente la invención está adema dirigida a compuestos y sales farmacéuticamente aceptables de Fórmula I en donde

R es oxígeno o está ausente

Ar se escoge de

fenilo que es mono di o tri-sustituido con R_A y 1 naftilo 2-naftilo piridilo pirimidinilo pirazinilo pindizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono- di o tri sustituido con R_A

el grupo



representa un sistema de anillo saturado insaturado o aromático que comprende 0 o 1 heteroátomos en donde

Z_1 es CR_1 o CR_1R_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 o CR_3R_3

R_1 se escoge de

i) halógeno hidroxi ciano amino alquilo C_1 C_{10} O(alquil C_1 C_6) mono o di(alquil C_1-C_6)amino (cicloalquil C_3-C_7) alquilo C_1-C_4 halo (C_1 C_6) alquilo O(halo (C_1-C_6) alquilo) y S(O) (alquilo C_1 C_6) -O(cicloalquilo C_3-C_7) alquilo C_1 C_4 y

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S(O) (alquilo C_1 C_6) donde cada alquilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1 C_4 y mono- o di (C_1-C_4) alquilamino

y

donde cada cicloalquilo C_3 C_7 es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1-C_4 y mono-o di (C_1-C_4) alquilamino y

ii) fenilo que es mono- di o tri-sustituido con R_A 1 naftilo 2 naftilo piridilo dihidropiridilo tetrahidropiridilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido con R_A

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1 C_3 halo (C_1 C_3) alquilo alcoxi C_1 C_3 amino (C_1 C_3) alquilo y mono y di (C_1-C_6) alquilamino

R_1 R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1-C_6 halo (C_1-C_6) alquilo y amino (C_1-C_6) alquilo

R_2 se escoge de hidrógeno alquilo C_1 C_6 halo (C_1-C_6) alquilo y amino (C_1-C_6) alquilo

Z_4 es NR o CR_4

Z_5 es NR o CR_5

R_4 y R_5 son independientemente escogidos de hidrógeno halógeno ciano nitro amino mono o di (carbhidrilo C_1-C_8) amino carbhidrilo C_1 C_8 (ciclocarbhidrilo C_3 C_7) carbhidrilo C_0-C_4 O(ciclocarbhidrilo C_3-C_7) halo(C_1-C_8) carbhidrilo O(halo (C_1 C_8)carbhidrilo -O(carbhidrilo C_1-C_8) y S(O) (carbhidrilo C_1 C_8) donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono- y di (C_1 C_4) alquilamino y

donde cada carbhidrilo C_3 C_7 es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1-C_4 y mono- y di (C_1-C_4) alquilamino

R_A es independientemente seleccionada en cada ocurrencia de halógeno ciano nitro halo (C-C_8) alquilo halo (C_1 C_8) alcoxi hidroxi amino alquilo C_1-C_8 sustituido con 0-2 R_B alquenilo C_2-C_8 sustituido con 0-2 R_B alquinilo C_2-C_8 sustituido con 0 2 R_B cicloalquilo C_3-C_7 sustituido con 0 2 R_B (cicloalquilo C_3-C_7) alquilo C_1 C_4 sustituido con 0-2 R_B alcoxi C_1 C_8 sustituido con 0-2 R_B NH(alquilo C_1 C_8) sustituido con 0 2 R_B N(alquilo C_1 C_8)(alquilo C_1-C_8) cada alquilo C_1-C_8 independientemente sustituido con 0 2 R_B XR_C y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1-C_4 -O(alquil C_1-C_4) NH(alquilo C_1 C_4) N(alquilo C_1 C_4)(alquilo C_1 C_4) -S(O)n(alquilo) halo (C_1 C_4)

alquilo halo(C_1-C_4) alcoxi CO(alquilo C_1 C_4) CONH(alquilo C_1 C_4) CON(alquilo C_1 C_4)(alquilo C_1 C_4) XR_C y Y

Rc y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia de

hidrógeno y

grupos alquilo rectos ramificados o cíclicos que incluyen grupos (cicloalquil) alquilo que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contienen cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituido con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1-C_8 NH(alquilo C_1 C_8) N(alquilo C_1-C_8)(alquilo C_1 C_8) NHC(=O)(alquilo C_1 C_8) N(alquilo C_1-C_8)C(=O)(alquilo C_1 C_8) NHS(O) (alquilo C_1-C_8) -S(O) (alquilo C_1 C_8) S(O) NH(alquilo C_1 C_8) S(O) N(alquilo C_1 C_8)(alquilo C_1-C_8) y Z

X es independientemente seleccionado en cada ocurrencia del grupo que consiste de -CH2 -CHR_D- O -C(=O) -C(=O)O -$S(O)_n$- NH NR_D- C(=O)NH C(=O)NR_D- -S(O) NH -S(O) NR_D- OC(=S)S NHC(=O) NR_DC(=O)- NHS(O) $OSiH_2$- -OSiH(alquilo C1 C4) OSi (alquilo C_1-C_4)(alquilo C_1-C_4) y NR_DS(O)

Y y Z son independientemente seleccionado en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituido con uno o más sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino

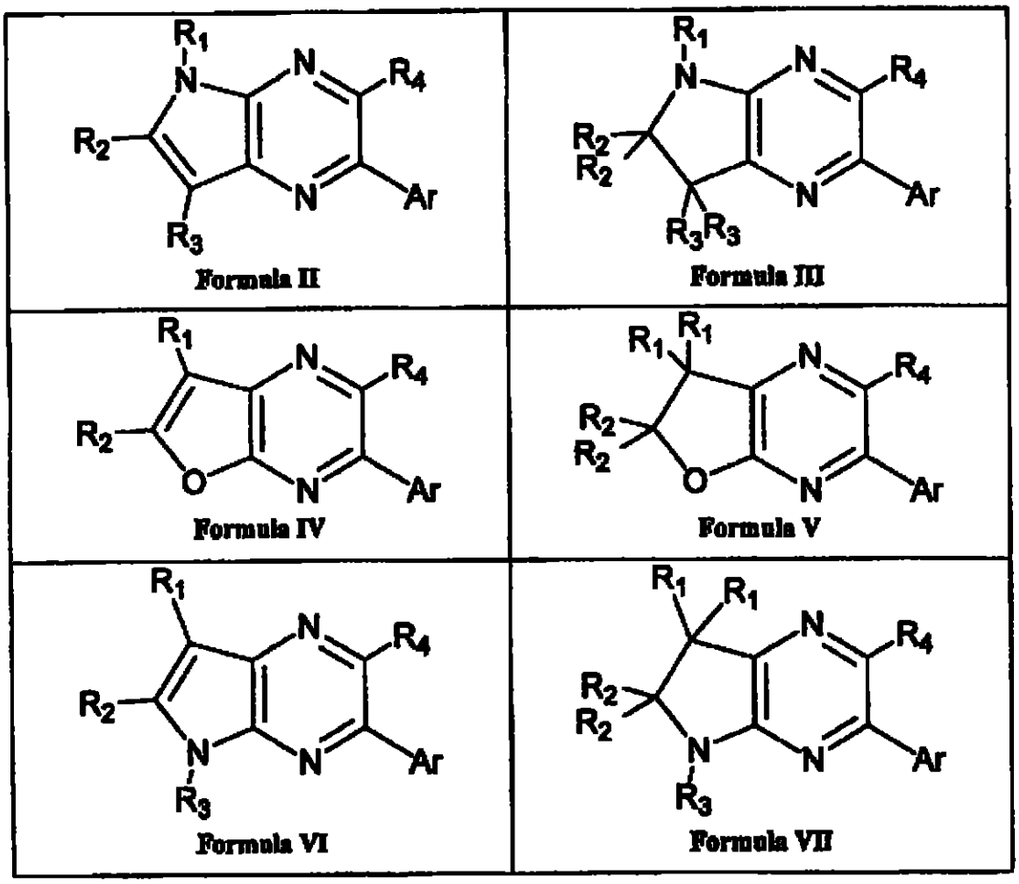
ciano alquilo C_1-C_4 -O(alquilo C_1-C_4) NH(alquilo C_1-C_4) N(alquilo C_1 C_4)(alquilo C_1-C_4) y S(O) (alquilo) en donde dicho grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S con el punto de unión siendo el carbono o nitrógeno

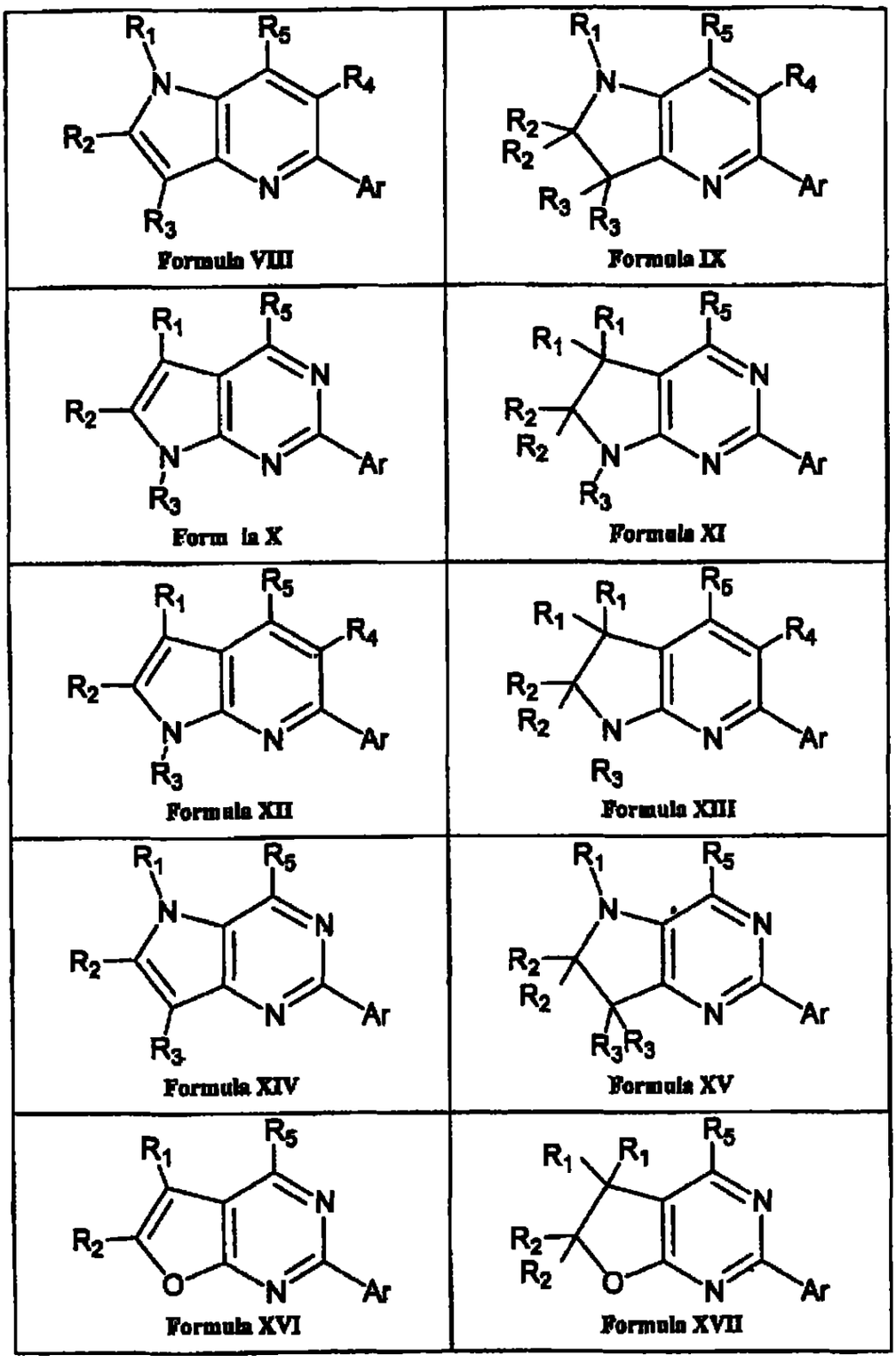
y n es independientemente seleccionado en cada ocurrencia de 0 1 y 2 Tales compuestos se denominarán como compuestos de Fórmula I-c

Ciertos compuestos preferidos de Fórmula I c incluyen aquellos en los cuales al menos uno de Z_4 y Z_5 no es NR Ciertos otros compuestos preferidos de Fórmula I-c incluyen aquellos en los cuales Z_4 se selecciona de N y CR_4 y Z_5 se seleccionan de N y CR_5

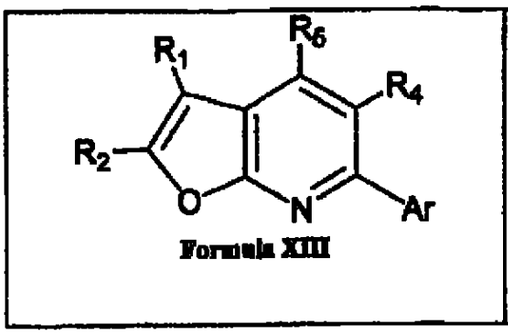
Modalidades particulares de la invención incluyen compuestos que tienen las siguientes fórmulas

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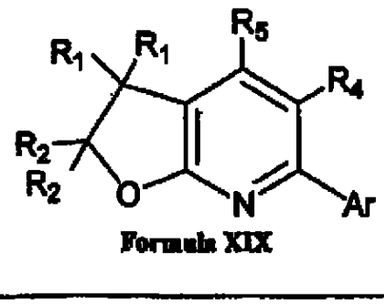

R1
N
R4
R2
Ar
R3
Formula II
R1
N
R4
R2
R2
Ar
R3R3
Formula III
R1
N
R4
R2
O
N
Ar
Formula IV
R1
R1
N
R4
R2
R2
O
N
Ar
Formula V
R1
N
R4
R2
N
N
Ar
R3
Formula VI
R1
R1
N
R4
R2
R2
N
N
Ar
R3
Formula VII


Formula VIII
Formula IX
Form la X
Formula XI
Formula XII
Formula XIII
Formula XIV
Formula XV
Formula XVI
Formula XVII

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Formula XIII



Formula XIX

Para cada uno de los compuestos y sales de la Fórmula II –Fórmula XIX R_1 R_1 R_1 R_2 R_2 R_2 R_3 R_3 R_3 R_4 R_5 y Ar son definidos anteriormente para la Fórmula I o preferiblemente son como se definieron anteriormente para la Fórmula I-a I b o I-c

Más preferiblemente

R_1 R_1 y R_1 son como se definió para la Fórmula I-a I-b o I-c

R_2 y R_3 son hidrógeno

R_2 (o R_2) se seleccionan de hidrógeno metilo y etilo

R_3 (o R_3) se seleccionan de hidrógeno y alquilo C_1 C_6 (o más preferiblemente R_3 o R_3 es alquilo C_1 C_3 cuando Z_1 es NR_1 o cuando Z_3 es NR_3

R_4 y R_5 son independientemente seleccionados de hidrógeno halógeno ciano amino alquilo C_1-C_6 alcoxi C_1-C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 (cicloalquilo C_3-C_7) alcoxi C_1-C_4 mono y di (alquilo C_1 C_6) amino amino(C_1 C_6) alquilo mono y di (alquilo C_1 C_6) amino (C C_6) alquilo halo (C_1 C_6) alquilo y halo (C_1-C_6)alcoxi y

Ar se selecciona del grupo que consiste de fenilo pirídilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1-C_6) halo (C_1-C_6) alcoxi

hidroxi amino alquilo C_1-C_8 alquenilo C_2-C_8 alquinilo C_2-C_8 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1-C_4 alcoxi C_1 C_8 mono y di (alquilo C_1 C_8)amino amino (C_1 C_8) alquilo y mono- y di (alquilo C_1 C_8)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula II Fórmula XX anterior es sustituido

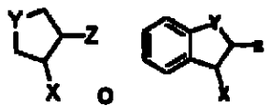
En ciertos compuestos preferidos de la Fórmula I (por ejemplo I-a y I b) y varias subfórmulas de estos que comprenden un grupo R_1 o R_1 el residuo R_1 o R_1 se selecciona de alquilo C_1C_{10} y (cicloalquilo C_3-C_7) alquilo C_0-C_4 cada uno de los cuales es sustituido con 0 o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1 C4 y mono- y di (C_1 C_4) alquilamino

En ciertos otros compuestos preferidos de la Fórmula I (por ejemplo I-a y I b) y varias subfórmulas de estos que comprenden un grupo R_1 o R_1 el residuo R_1 o R_1 se selecciona de heterocicloalquilo C_{3-9} y (heterocicloalquilo C_{3-9}) alquilo C_1 C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1 C_8 alcoxi C_1 C_8 hidroxialquilo C_1 C_8 alcoxi C_1-C_8 alquilo C_1 C_8 haloalquilo(C_1-C_8) haloalcoxi(C_1-C_8) mono- y di (C_1-C_8) alquilamino XR_C Ciertos grupos heterocicloalquilo C_{3-9} y alquilo C_1 C_4(heterocicloalquilo C_{3-9}) incluyen aquellos escogidos de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales es sustituido con de 0 a 2 sustituyentes independientemente escogidos de (i) halógeno hidroxi amino ciano o (ii) alquilo C_1 C_4 alcoxi C_1 C_4 y mono y di (C_1-C_4) alquilamino cada uno de los cuales

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sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-9}

Ciertos otros compuestos preferidos de Fórmula I (por ejemplo I-a o I b) y compuestos de Fórmula II XIX incluyen aquellos compuestos en los cuales R_1 o R_1 se seleccionan de 3-pentil 2 butil 1 metoxi but 2 ilo 1-dimetilamino-but 2 ilo 3- (tiazol 2 ilo) 1H pirazol 1 ilo y grupos de formula



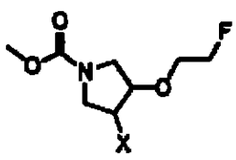
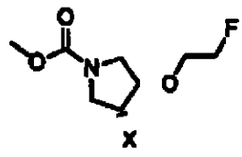
en donde X es el punto de unión del nitrógeno y el anillo de imidazo

Y se selecciona de CH_2 O S S(O) SO_2 NC_1 C8alquilo (que incluyen grupos alquilo lineales y ramificados) NC_1 C_8haloalquilo NC_3 C_8cicloalquilo NC(O) alquilo C_1 C_8 (que incluyen grupos alquilo lineales y ramificados) NC(O) haloalquilo C_1-C_8 NC(O) cicloalquilo C_3 C_8 N benzoilo N benzilo $NCOOC_1$ C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) $NCOOC_1$-C_8 haloalquilo $NCOOC_3$-C_8 Cicloalquilo y

Z se selecciona de hidrógeno hidroxi amino NC_1 C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) NHC_1-C_8 haloalquilo NHC_3-C_8 cicloalquilo $NHC(O)C_1$ C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) $NHC(O)C_1$ C_8 haloalquilo $NHC(O)C_3$-C_8 cicloalquilo NH benzoilo NH benzilo $NHCOOC_1$ C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) $NHCOOC_1$-C_8 haloalquilo $NHCOOC_3$ C_8 cicloalquilo alcoxi C_1-C_8 (que incluyen lgrupos alcoxi lineales y ramificados) haloalcoxi C_1 C_8 cicloalcoxi C_3-C_8 OC(O) alquilo C_1-C_8 (que incluyen grupos alquilo lineales y ramificados) OC(O)

haloalquilo C_1-C_8 OC(O) cicloalquilo C3-C8 benzoiloxi benziloxi $OCONHC_1$ C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) $OCONHC_1$-C_6 haloalquilo $OCONHC_3$-C_8 cicloalquilo alquilotio C_1-C_8 (que incluyen grupos alquilo lineales y ramificados) haloalquiltio C_1 C_8 cicloalquiltio C_3 C_8 S(O) C_1 C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) S(O)C_1 C_8haloalquilo S(O) C_3 C_8 cicloalquilo SO_2 C_1 C_8 alquilo (que incluyen grupos alquilo lineales y ramificados) SO_2C_1-C_8 haloalquilo SO_2C_3-C_8Cicloalquilo

En aun otros aspectos los compuestos preferidos de la Fórmula I (por ejemplo I-a o 1 b) y los compuestos de Formulae II XIX incluyen aquellos compuestos en los cuales R_1 o R_1 son seleccionados de

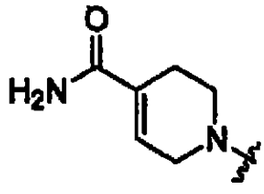



o más preferiblemente un grupo de fórmula

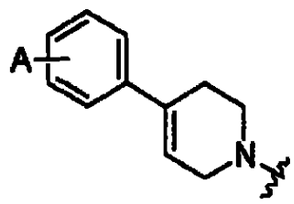
en donde X es el punto de unión del te nitrógeno del anillo imidazo

Los grupos R_1 particularmente preferidos son mostrados en la Matriz $R_2$2 y los grupos R_1 particularmente preferidos son mostrados en la Matriz $R_1$2 ambos en el Ejemplo 1 que sigue

Otros grupos R_1 preferidos incluyen grupos de fórmula

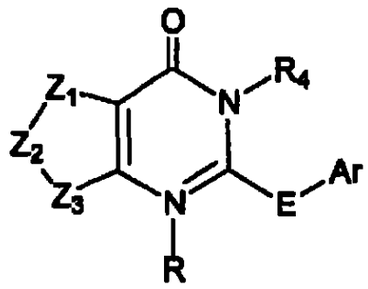


y grupos de fórmula



en donde A representa hasta tres grupos independientemente escogidos de hidrógeno halógeno alquilo y alcoxi

Otra modalidad de la invención está dirigida a los compuestos de Fórmula XX



Fórmula XX

o una sal farmacéuticamente aceptable de esta en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1-C_4

m es 0 1 o 2

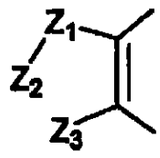
Ar se escoge de

fenilo que es mono- di- o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono di o tri-sustituido y opcionalmente heteroarilo mono di- o tri-sustituido dicho heteroarilo que tiene de 1 a aproximadamente 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a

aproximadamente 3 heteroátomos seleccionados del grupo que consiste de N O y S

R es oxígeno o está ausente

el grupo



representa un sistema de anillo de 5 miembros saturado insaturado o aromático que contiene 0 o 1 heteroátomos en donde

Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 CR_3R_3 o NR3

R_1 se escoge de halógeno hidroxi ciano amino alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido alcoxi opcionalmente sustituido mono o dialquilamino opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido cicloalquilo opcionalmente sustituido heterocicloalquilo opcionalmente sustituido alquiltio opcionalmente sustituido alquilsulfinilo opcionalmente sustituido alquilsulfonilo opcionalmente sustituido mono-o dialquilcarboxamida opcionalmente sustituido anilo carbocíclico opcionalmente sustituido y heteroanilo opcionalmente sustituido dicho heteroarilo opcionalmente sustituido tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionados del grupo que consiste de N O y S

R1 se escoge de alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido cicloalquilo opcionalmente sustituido heterocicloalquilo opcionalmente sustituido (heterocicloalquil) alquilo opcionalmente sustituido arilo carbocíclico opcionalmente sustituido y heteroarilo opcionalmente sustituido dicho heteroarilo opcionalmente sustituido tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a 3 heteroátomos seleccionados del grupo que consiste de N O y S

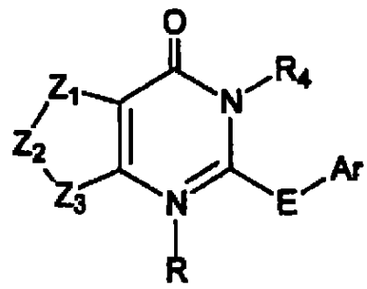
R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo haloalquilo alcoxi aminoalquilo y mono y dialquilamino

R R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo haloalquilo y aminoalquilo

R_2 y R_3 son independientemente escogidos de hidrógeno alquilo haloalquilo y aminoalquilo y

R_4 es hidrógeno alquilo aminoalquilo y haloalquilo

Ciertos otros compuestos preferidos y sales farmacéuticamente aceptables de la invención incluyen aquellos compuestos de Fórmula XX



FórmulaXX

o una sal farmacéuticamente aceptable de esta en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1 C_4

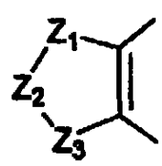
m es 0 1 o 2

R es oxígeno o está ausente

Ar se escoge de

fenilo que es mono di- o tri sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido y opcionalmente heteroarilo mono di o tri-sustituido dicho heteroarilo que tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a 3 heteroátomos seleccionados del grupo que consiste de N O y S

el grupo



representa un sistema de anillo saturado insaturado o aromático que contiene 0 o 1 heteroátomos en donde

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Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 CR_3R_3 o NR3

R_1 se escoge de

i) halógeno hidroxi ciano amino carbihidrilo C_1 C_{10} O(carbihidrilo C_1-C_8) mono o di (carbihidrilo C_1 C_8)amino (ciclocarbihidrilo C_3-C_7) carbihidrilo C_1 C_4 halo (C_1 C_8) carbihidrilo O(halo (C_1 C_8) carbihidrilo) y S(O) (carbihidrilo C_1 C_8) O(ciclocarbihidrilo C_3-C_7) carbihidrilo C_1-C_4 heterocicloalquilo C_{3-9} (heterocicloalquilo C_{3-9}) alquilo C_1-C_4 y S(O) (carbihidrilo C_1 C_8) donde cada carbihidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triple enlaces donde cada heterocicloalquilo tiene 1 o 2 heteroátomos en el anillo seleccionados de N O o S y el punto de unión es carbono o nitrógeno y

donde cada carbihidrilo heterocicloalquilo o ciclocarbihidrilo es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1 C_8 alcoxi C_1 C_8 haloalcoxi C_1 C_8 alcanoilo C_1-C_8 alcanoiloxi C_1-C_8 alcoxicarbonilo C_1-C_8 N-(alcanoilo C_1-C_8) N (alquilo C_0-C_8)amino N (alcanoiloxi C_1-C_8) N (alquilo C_0-C_8)amino N (alcoxicarbonilo C_1 C_8) N (alquilo C_0-C_8)amino alquilsulfonamida C1 C_8 alquilosulfonilo C_1-C_8 alquilosulfoniloxi C_1 C_8 hidroxialquilo C_1 C_8 alcoxi C_1 C_8 alquilo C_1-C_8 haloalcoxi C_1-C_8 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono- y di (C_1-C_8) alquilamino N (alcanoilo C_1 C_8) N-(alquil C_0-C_8)amino N (alcanoiloxi C_1-C_8) N (alquil C_0-C_8) amino N (alcoxicarbonilo C_1 C_8)-N (alquil C_0-C_8) amino mono- y di (C_1 C_8) alquilcarbamoilo XR_C y X Z y

ii) fenilo que es mono di o tri-sustituido con R_A 1 naftilo 2 naftilo piridilo dihidropiridilo tetrahidropiridilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales es opcionalmente mono- di- o tri sustituido con R_A

R_1 se escoge de

alquiloC_1-C_{10} alquenilo C_2-C_{10} alquinilo C_2-C_{10} cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7) alquilo C_1-C_4 heterocicloalquilo C_{3-9} (heterocicloalquilo C_{3-9}) alquilo C_1 C_4 y halo (C_1 C_6) alquilo cada uno de los cuales es sustituido con 0 o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1-C_6 alcoxi C_1-C_6 haloalcoxi C_1-C_6 alcanoilo C_1-C_6 alcanoiloxi C_1 C_6 alcoxicarbonilo C_1 C_6 N (alcanoilo C_1 C_6) N (alquil C_0-C_6) amino N (alcanoiloxi C_1-C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1 C_6) N (alquilo C_0-C_6) amino alquilo sulfonamida C_1 C_6 alquilsulfonilo C_1-C_6 alquilsulfoniloxi C_1 C_6 hidroxialquilo C_1-C_6 alcoxi C_1 C_6 alquilo C_1-C_6 haloalcoxi C_1 C_6 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono y di (C_1 C_6) alquilamino N (alcanoilo C_1 C_6) N (alquilO C_0-C_6) amino N-(alcanoiloxi C_1 C_6) N (alquilo C_0-C_6) amino N (alcoxicarbonilo C_1 C_6) N (alquilo C_0-C_6) amino mono y di-alquilcarbamoilo (C_1 C_6) XRc y X Z

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1-C_6 halo (C_1 C_6) alquilo alcoxi C_1 C_6 amino (C_1 C_6) alquilo y mono y di (C_1-C_6) alquilamino

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1 C_6 halo (C_1-C_6) alquilo y amino (C_1 C_6) alquilo

R_2 y R_3 son independientemente escogidos de hidrógeno alquilo C_1 C_8 halo (C_1 C_8) alquilo y amino (C_1-C_8) alquilo

R_4 es hidrógeno alquilo C_1 C_8 aminoalquilo C_1 C_8 y haloalquilo C_1-C_8

R_A es independientemente seleccionado en cada ocurrencia de halógeno ciano nitro halo (C_1 C_8) alquilo halo (C_1-C_8) alcoxi hidroxi amino alquilo C_1-C_8 sustituido con 0 2 R_B alquenilo C_2-C_8 sustituido con 0 2 R_B alquinilo C_2-C_8 sustituido con 0 2 R_B cicloalquilo C_3-C_7 sustituido con 0 2 R_B (cicloalquilo C_3-C_7) alquilo C_1-C_4 sustituido con 0 2 R_B alcoxi C_1 C_8 sustituido con 0 2 R_B NH(alquilo C_1 C_8) sustituido con 0 2 R_B N(alquilo C_1 C_8)(alquilo C_1-C_8) cada alquilo C_1-C_8 independientemente sustituido con 0 2 R_B XRc y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1 C_4 O(alquilo C_1-C_4) NH(Cz C_4alquilo) N(alquilo C_1-C_4)(alquilo C_1 C_4) S(O) (alquilo) halo (C_1 C_4) alquilo halo (C_1 C_4) alcoxi CO(alquilo C_1 C_4) CONH(alquilo C_1 C_4) CON(alquilo C_1 C_4)(alquilo C_1 C_4) XR_C y Y

R_c y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia de hidrógeno y

grupos alquilo rectos ramificados o cíclicos que incluyengrupos (cicloalquil) alquilo que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contiene cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituido

con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1 C_6 NH(alquilo C_1-C_6) N(alquilo C_1-C_6)(alquilo C_1-C_6) NHC(=O)(alquilo C_1-C_6) N(alquilo C_1 C_6)C(=O)(alquilo C_1 C_6) NHS(O) (alquilo C_1 C_6) S(O) (alquilo C_1 C_6) -S(O) NH(alquilo C_1-C_6) S(O) N(alquilo C_1 C_6)(alquil C_1-C_6) y Z

X es independientemente seleccionado en cada ocurrencia del grupo que consiste de CH2 -CHRD -0 -C(=O) C(=O) O- S(O) NH NR_D- C(=O)NH C(=O)NR_D- -S(O) NH S(O) NR_D- -OC(=S)S- NHC(=O) NR_DC(=O) NHS(O) $OSiH_2$- -OSiH(alquilo C_1-C_4) OSi(alquilo C_1 C_4) (alquilo C_1-C_4) y NR_DS(O)

Y y Z son independientemente seleccionado en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituidos con uno o más sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino ciano alquilo C_1 C_4 O(alquilo C_1-C_4) C(O)(alquilo C_1 C_4) NH(alquilo C_1 C_4) N(alquilo C_1 C_4)(alquilo C_1 C_4) yS(O) (alquilo) en donde dicho grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S con el punto de unión siendo carbono o nitrógeno y

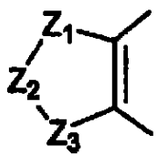
n es independientemente seleccionado en cada ocurrencia de 0 1 y 2

Los compuestos prefendos y sales farmacéuticamente aceptables de la Fórmula XX son aquellos para los cuales

Ar se escoge de

fenilo que es mono- di o tri-sustituido con R_A y 1 naftilo 2 naftilo piridilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales es opcionalmente mono- di o tri sustituido con R_A

el grupo



representa un sistema de anillo saturado insaturadoo arómatico que comprende 0 o 1 heteroátomos

en donde

Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 CR_3R_3 o NR3

R_1 se escoge de

i) halógeno hidroxi ciano amino carbhidrilo C_1-C_{10} O(carbhidrilo C_1 C_8) mono o di (carbhidrilo C_1 C_8)amino (cicloalquilo C_3 C_7) carbhidrilo C_1-C_4 halo (C_1 C_8) carbhidrilo O(halo (C_1 C_8) carbhidrilo) y S(O) (carbhidrilo C_1 C_8) O(cicloalquilo C_3-C_7) carbhidrilo C_1 C_4 y S(O) (carbhidrilo C_1 C_8)

donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido por

uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1 C_1 C_4 y mono- o di alquilamino C_1 C_4

y

donde cada cicloalquilo C_3C_7 es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1 C_4 y mono- o di alquilamino C_1-C_4

y

ii) fenilo que es mono- di o tri-sustituido con R_A 1 naftilo 2 naftilo pirídilo dihidropirídilo tetrahidropirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido con R_A

R_1 se escoge de

carbhidrilo C_1 C_{10} (cicloalquilo C_3 C_7) carbhidrilo C_1 C_4 halo (C1C6) carbhidrilo donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1 C_4 y mono-o di (C_1-C_4) alquilamino y donde cada cicloalquilo C_3-C_7 es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1 C_4 y mono-o di (C1-C_4) alquilamino

y

ii) fenilo que es mono- di o tri-sustituido con R_A 1 naftilo 2 naftilo pirídilo dihidropirídilo tetrahidropirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo

oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono- di o tri sustituido con R_A

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1 C_6 halo (C_1-C_6) alquilo alcoxi C_1 C_6 amino (C1-C_6) alquilo y mono y di (C_1 C_6) alquilamino

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1 C_6 halo (C_1 C_6) alquilo y amino (C_1 C_6) alquilo

R_2 y R_3 son independientemente escogidos de hidrógeno alquilo C_1 C_6 halo (C_1 C_6) alquilo y amino (C_1-C_6) alquilo

R_4 es hidrógeno o C1 C_6alquilo

R_A es independientemente seleccionado en cada ocurrencia de halógeno ciano nitro halo (C_1 C_6) alquilo halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1-C_6 sustituido con 0-2 R_B alquenilo C_2-C_6 sustituido con 0 2 R_B alquinilo C_2-C_6 sustituido con 0-2 R_B cicloalquilo C_3 C_7 sustituido con 0-2 R_B (cicloalquilo C_3 C_7) alquilo C_1 C_4 sustituido con 0-2 R_B alcoxi C_1 C_6 sustituido con 0-2 R_B NH(alquilo C_1 C_6) sustituido con 0-2 R_B N(alquilo C_1 C_6)(alquilo C_1 C_6) cada alquilo C_1 C_6 independientemente sustituido con 0-2 R_B XR_C y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1-C_4 O(alquilo C_1 C_4) NH(alquilo C_1 C_4) N(alquiloC_1 C_4l)(alquilo C_1 C_4) S(O) (alquilo) halo (C_1-C_4)

alquilo halo (C_1 C_4) alcoxi CO(alquilo C_1 C_4) CONH (alquilo C_1 C_4) CON(alquilo C_1-C_4)(alquilo C_1-C_4) XR_C y Y

R_C y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia de

hidrógeno y

grupos alquilo rectos ramificados o cíclicos que incluyen grupos (cicloalquil) alquilo que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contienen cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituido con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1 C_6 NH (alquilo C_1-C_6) N(alquilo C_1-C_6)(alquilo C_1-C_6) NHC(=O)(alquilo C_1 C_6) N(alquilo C_1 C_6)C(=O)(alquilo C_1 C_6) NHS(O) (alquilo C_1 C_6) S(O) (alquilo C_1-C_6) -S(O) NH(alquilo C_1 C_6) S(O) N(alquilo C_1 C_6)(alquilo C_1 C_6) y Z

X es independientemente seleccionado en cada ocurrencia del grupo que consiste de CH2 $-CHR_D-$ O C(=O) -C(=O)O $S(O)_n-$ NH NR_D C(=O)NH $C(=O)NR_D-$ S(O) NH S(O) NR_D- OC(=S)S NHC(=O) $NR_DC(=O)$ NHS(O) $-OSiH_2$ -OSiH(alquilo C_1 C_4) OSi(alquilo C_1 C_4)(alquilo C_1 C_4) y $NR_DS(O)$

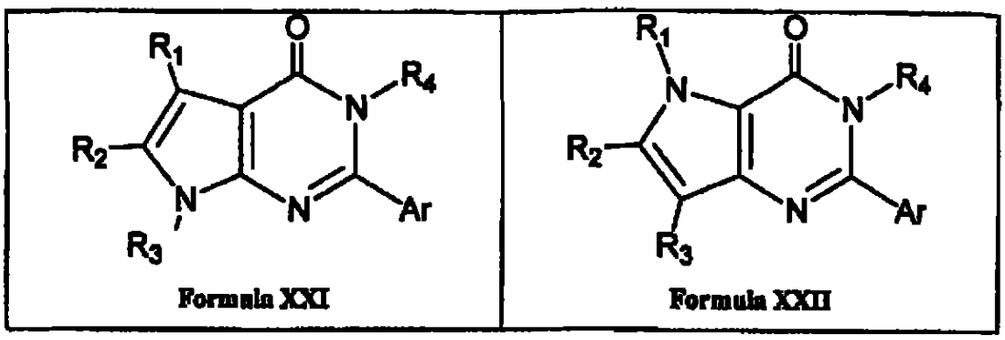
Y y Z son independientemente seleccionados en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituidos con uno o más sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino

ciano alquilo C_1-C_4 O(alquilo C_1-C_4) NH(alquilo C_1-C_4) N(alquilo C_1 C_4)(alquilo C_1 C_4) y S(O) (alquilo)

en donde dicho grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S con el punto de unión siendo carbono o nitrógeno y

n es independientemente seleccionado en cada ocurrencia de 0 1 y 2 Tales compuestos se denominarán como compuestos de Fórmula XXA

La invención está particularmente dirigida acompuestos y sales de la siguienete Fórmula



Formula XXI Formula XXII

Los compuestos preferidos y las sales de FórmulaXXI y FórmulaXXII

R_{1y} R_2 p rima son como se definió para la FórmulaXX o preferiblemente como se definió para la FórmulaXXA

R_2 se selecciona de hidrógeno metilo y etilo

R_3 se selecciona de hidrógeno y alquilo C_1C_6 y

Ar se selecciona del grupo que consiste de fenilo piridilo que es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (C_1-C_6) alquilo halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1-C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3-C_7 (cicloalquilo C_3-C_7) alquilo C_1 C_4 alcoxi C_1 C_6 mono- y di (alquilo C_1 C_6) amino amino(C_1 C_6) alquilo y mono- y di (alquilo C_1-C_6) amino en donde en
Ar al menos uno de la posción orto de el punto de unión de Ar mostrado en la Fórmula XXI o XXII se sustituye

Los compuestos de la invención son útiles para tratar una variedad de condiciones que incluyen desórdenes afectivos desórdenes de ansiedad desórdenes por estrés desórdenes alimenticios o desórdenes de comida y adicción a las drogas

Los desórdenes afectivos incluyen todo los tipos de depresión desorden bipolar ciclotimia y distimia

Los desórdenes de ansiedad incluyen desórdenes generalizados de ansiedad pánico fobias y desorden obsesivo-compulsivo

Desórdenes relacionados con tensión incluyen desorden por tensión post traumática tensión hemorrágica episodios sicóticos inducidos por tensión enanismo sicosocial dolores de cabeza por tensión desórdenes del sistema inmune inducidos por tensión tal como fiebre inducida por tensión y desórdenes de sueño relacionados con tensión

Desórdenes de comida que incluyen anorexia nerviosa bulita nerviosa y obesidad

Moduladores de los receptores CRF también son utiles en el tratamiento (por ejemplo tratamiento sintomático) de una variedad de desórdenes neurológicos que incluyen parálisis supranuclear demencia relacionada con SIDA demencia por multiinfarto desórdenes neurodegenerativos tal como enfermedad de Alzheimer enfermedad de Parkinson y enfermedad de Huntington trauma de cabeza trauma de cuerda espinal daño isquémico neuronal esclerosis lateral amiotrófica desórdenes de percepción del dolor tal como fibromialgia y epilepsia

Adicionalmente los compuestos de Fórmula I son útiles como moduladores del receptor CRF en el tratamiento (por ejemplo tratamiento sintomático) de un número de condiciones gastrointestinales cardiovasculares hormonales autoinmunes e inflamatorias Tales condiciones incluyen síndrome de intestino irritable úlceras enfermedad de Crohn colon aspático diarrea íleo post operativo e hipersensibilidad colónica asociada con disturbios o tensión psicopatológica hipertensión taquicardia falla cardiaca congestiva infertilidad síndrome de enfermedad de eutiroides condiciones inflamatorias efectuadas por artritis reumatoide y osteoartritis dolor asma soriasis y alergias

Los compuestos de Fórmula I también son utiles como moduladores del receptor CRF1 en el tratamiento de desórdenes animales asociados con nivel de CRF aberrantes Estas condiciones incluyen síndrome de estrés porcino fiebre del envió de bovinos fibriación paroxismal de equino y disfunciones inducidas por confinamiento en pollos tensión por golpes en ovejas o interacción humana animal relacionado con tensión en perros enanismo sicosocial e hipoglicemia

Los sujetos típicos a los cuales los compuestos de la invención se pueden administrar serán mamíferos particularmente primates especialmente humanos Para aplicaciones veterinarias una amplia variedad de sujetos será adecuada por ejemplo ganado tal como reses ovejas cabras vacas cerdos y similares aves tales como pollo patos gansos pavos y similares y otros animales domesticados particularmente mascotas como perros y gatos Para el diagnóstico o aplicaciones de investigación una amplia variedad de mamíferos serán sujetos adecuados que incluyen roedores (por ejemplo ratones ratas hámsteres) conejos primates y cerdos tales como marranos sin mezcla y similares Adicionalmente para aplicaciones in vitro tales diagnósticos in vitro y aplicaciones de investigación fluidos de cuerpo (por ejemplo sangre plasma suero CSF linfa fluido intersticial celular humor acuoso saliva fluido sinovial heces u orina) y muestras de células y tejidos de los sujetos anteriores será adecuados para uso

Los compuestos de unión CRF suministrados por esta invención y los derivados marcados de estos son útiles también estándares y reactivos para determinar la capacidad de los compuestos de ensayo (por ejemplo un potencial farmacéutico) para unirse a un receptor CRF

Los compuestos antagonistas CRF de los derivados marcados suministrados por esta invención son también utiles como radiotrazadores para imágenes de tomografía de emisión de positrones (PET) y para tomo grafía computarizada de emisión de fotones simple (SPECT)

Los compuestos más particulares de la invención pueden ser utilizados para demostrar la presencia de receptores CRF en muestras de célula o tejido Esto se puede hacer para preparar una pluralidad de muestras de célula o tejido

coincidente al menos una de las cuales está preparada como una muestra de experimento y al menos una de las cuales está preparada como una muestra de control La muestra experimental se prepara al poner en contacto (bajo condiciones que permiten la unión de los receptores CRF a CRF dentro de las muestras de célula y tejido) al menos una de las muestras de célula o tejido coincidentes que no se ha contactado previamente con ningún compuesto o sal de la invención con una solución experimental que comprende la preparación detectablemente marcada del compuesto o la sal seleccionada en una primer concentración molar medida La muestra de control se prepara de la misma manera que la muestra experimente y es incubada en una solución que contiene los mismos ingredientes que la solución experimental pero que también contiene una preparación no marcada del mismo compuesto o sal de la invención a una concentración molar que es mayor que la primera concentración molar medida

Las muestras experimentales y de control son entonces lavadas para remover un compuesto detectablemente marcado no unido La cantidad de compuesto detectablemente marcado que permanece unido en cada muestra es luego medida y la cantidad de compuesto detectablemente marcado en las muestras experimentales y de control se compara Una comparación que indica la detección de una mayor cantidad de marca detectable en al menos una muestra experimental lavada que es detectada en cualquiera de al menos una de las muestras de control lavada demuestra la presencia de receptores CRF en esa muestra experimental

El compuesto detectablemente marcado utilizado en este procedimiento se puede marcar con cualquier marca detectable tal como una marca radioactiva una etiqueta biológica tal como biotina (que puede ser detectada por unión a avidita

detectablemente marcada) una enzima (por ejemplo alcalino fosfatasa beta galactosidasa o una enzima similar cuya actividad puede ser detectada en un ensayo colorimétrico) o una marca directa o indirectamente luminiscente Cuando la secciones de tejido son utilizadas en este procedimiento y el compuesto detectablemente marcado se radiomarca la unión el compuesto marcado se puede detectar autoradiográficamente para generar un autoradiograma Cuando se utiliza la autoradiografía la cantidad de marca detectable en una muestra experimental o de control se puede medir al ver los autoradiogramas y comparar la densidad de exposición de los autoradiogrmas

La presente invención también corresponde a métodos para inhibir la unión de CRF a receptores CRF (preferiblemente receptores CRF1) cuyos métodos involucran poner en contacto una solución que contiene un compuesto antagonista CRF de la invención con células que expresan receptores CRF en donde el compuesto está presente en la solución en una concentración suficiente para inhibir la unión de CRF a los receptores CRF in vitro Este método incluye inhibir la unión del CRF a los receptores CRF in vivo por ejemplo en un paciente dada una cantidad de un compuestos de Fórmula I que sería suficiente para inhibir la unión del CRF a los receptores CRF in vitro En una modalidad tales métodos son útiles para tratar desórdenes fisiológicos asociados con concentraciones en exceso de CRF La cantidad de un compuesto que sería suficiente para inhibir la unión de un CRF al receptor CRF se puede determinar fácilmente por vía del ensayo de unión del receptor CRF (ver por ejemplo Ejemplo 51) o desde el EC_{50} de un ensayo funcional del receptor CRF tal como un ensayo estándar de quimiotaxis mediada por receptor CRF Los receptores CRF utilizados para determinar la unión in vivo se pueden obtener de una variedad de fuentes por ejemplo de células que

expresan naturalmente los receptores CRF por ejemplo las células IMR32 o de las células que expresan receptores CRF humanos clonados

La presente invención también corresponde a métodos para alterar la actividad de los receptores CRF dichos métodos comprenden exponer las células que expresan tales receptores a una cantidad efectiva del compuesto de la invención en donde el compuesto está presente en una solución a una concentración suficiente para alterar específicamente la actividad de transducción de la señal en respuesta al CRF en células que expresan receptores CRF en vitro las células preferidas para este propósito son aquellas que expresan altos niveles de receptores CRF (es decir iguales o mayores que el numero de receptores CRF1 por célula encontrada en células de neuroblastoma humana IMR-32 diferenciadas) siendo las células IMR 32 particularmente preferidas para ensayar la concentración de un compuesto requerido para alterar la actividad de los receptores CRF1 este método incluye alterar la actividad de transducción de señal de los receptores CRF in vivo por ejemplo en un paciente dada una cantidad de un compuestos de Fórmula I que sería suficiente para alterar la actividad de transducción de señal en respuesta al CRF en las células que expresan receptores CRF in vitro La cantidad de un compuesto que sería suficiente para alterar la actividad de transducción de la señal en respuesta al CRF o a los receptores CRF también se puede determinar por via de un ensayo del receptor CRF mediado por transducción de señal tal como un ensayo en donde la unión del CRF a un receptor de CRF de superficie de célula efectua un cambio en la expresión del gen reportero

La presente invención también corresponde a una composición farmacéutica empacada para tratar desórdenes responsables de la modulación del receptor

CRF por ejemplo desórdenes de comida depresión o tensión La composición farmacéutica empacada incluye un recipiente que mantiene una cantidad terapéuticamente efectiva de al menos un modulador receptor CRF1 como se describió supra e instrucciones para utilizar el desorden de tratamiento responsable de la modulación del receptor CRF en el paciente

Descripción química y terminología

Los compuestos descritos aquí pueden tener uno o más centros o planos asimétricos Los compuestos de la presente invención contienen un átomo asimétricamente sustituido que puede ser aislado en formas ópticamente activa o racémica Es bien conocido en la técnica como preparar formas ópticamente activas tales como mediante resolución de formas racémicas (racematos) mediante síntesis asimétrica o mediante síntesis de materiales de partida ópticamente activos La resolución de los racematos se puede lograr por ejemplo mediante métodos convencionales tal como cristalización en la presencia de un agente de resolución o cromatografía utilizando por ejemplo una columna HPLC quiral Muchos isómeros geométricos de olefinas C=N dobles enlaces y similares pueden estar presentes en los compuestos descritos aquí y todos los tales isómeros estables están contemplados en la presente invención Los isómeros geométricos *Cis* y *trans* de los compuestos de la presente invención son descritos y se pueden aislar como una mezcla de isómeros o como formas isométricas separadas Todas las formas quirales (enantioméricas y diastereoméricas) y racémicas así como también todas las formas isoméricas geométricas de una estructura se pretenden a menos que la estereoquímica específica o la forma isomérica sea indicada específicamente

Cuando ocurre cualquier variable más de una vez en cualquier constituyente o fórmula para un compuesto su definición en cada ocurrencia es independiente de su definición en cada una de las otras ocurrencias Así por ejemplo si un grupo es mostrado por ser sustituido con 0-2 R entonces dicho grupo opcionalmente puede ser sustituido con hasta dos grupos R y R en cada ocurrencia se selecciona independientemente de la definición de R También las combinaciones de sustituyentes y/o variables son permisibles solamente si tales combinaciones resultan en compuestos estables

La Fórmula I incluye pero no está limitada a los compuestos de Fórmula I IA y II XXII Como se indica anteriormente varios sustituyentes de las varias fórmulas (compuestos de Fórmula I IA y II XXII son opcionalmente sustituidos incluyendo Ar^1 Ar^2 R^1 R^2 y R^3 de la Fórmula I y sub fórmulas de estas y tales sustituyentes son citados en las sub fórmulas tal como la sub fórmua I y las sub fórmulas El término sustituido como se utiliza aquí significa que uno cualquiera o más hidrógenos sobre el átomo o grupo designado se reemplaza con una selección del grupo indicado de sustituyentes siempre y cuando la valencia normal del átomo designado no se exceda y la sustitución de cómo resultado un compuesto estable Cuando un sustituyente es oxo (ceto es decir =0) entonces se reemplazan dos hidrógenos sobre un átomo La presente invención está destinada a incluir todos los isótopos (incluyendo radioisótopos) de átomos que ocurran en los presentes compuestos

Cuando sustituyentes tales como Ar R_1 R_2 R_3 R_4 y R_5 son adicionalmente sustituidos ellos pueden ser así sustituidos en una o más posiciones disponibles típicamente una a tres o cuatro posiciones por uno o más grupos adecuados tales como aquellos descritos aquí Los grupos adecuados que pueden estar presentes

en un Ar R_1 R_2 R_3 R_4 y R_5 sustituidos o otros grupos incluyen por ejemplo halógeno ciano hidroxilo nitro ácido alcanoilo (tal como grupos alcanoilo C_1-C_6 tal como acilo o similares) carboxamido grupos alquilo (que incluyen grupos cicloalquilo que tienen 1 a 8 átomos de carbono preferiblemente 1 2 3 4 5 o 6 átomos de carbono) grupos alquenilo y alquinilo (que incluyen grupos que tienen 1 o más enlaces insaturados de 2 a aproximadamente 8 preferiblemente 2 3 4 5 o 6 átomos de carbono) grupos alcoxi que tienen uno o más enlaces oxígeno y de 1 a aproximadamente 8 preferiblemente 1 2 3 4 5 o 6 átomos de carbono ariloxi tales como fenoxi grupos alquiltio que incluyen aquellos que tienen uno o más enlaces tioeter y de 1 a 8 átomos de carbono preferiblemente 1 2 3 4 5 o 6 átomos de carbono grupos alquilsulfinilo que incluyen aquellos que tienen uno o más enlaces sulfiniloy de 1 a 8 átomos de carbono preferiblemente 1 2 3 4 5 o 6 átomos de carbono grupos alquilsulfonilo que incluyen aquellos que tienen 1 o más enlaces sulfonilo y de 1 a aproximadamente 8 átomos de carbono preferiblemente 1 2 3 4 5 o 6 átomos de carbono grupos aminoalquilo que incluyen grupos que tienen uno o más átomos N y de 1 a aproximadamente 8 preferiblemente 1 2 3 4 5 o 6 átomos de carbono arilo carbocíclico que tiene 6 o más carbonos y uno o más anillos (por ejemplo fenilo bifenilo naftilo o similares cada anillo aromático sustituido o no sustituido) arilalquilo que tiene 1 a 3 anillos separados o fusionados y desde 6 a 18 átomos de carbono por anillo siendo el bencilo un grupo arilaquilo preferido arilalcoxi que tiene 1 a 3 anillos separados o fusionados y de 6 a aproximadamente 18 átomos de carbono por anillo como O bencilo siendo un grupo alcoxi preferido o un grupo heterocíclico saturado insaturado o aromático que tiene 1 a 3 anillos separados o fusionados con 3 a 8 miembros por anillo y 1 o más átomos N O o S por ejemplo coumarinilo quinolinilo isoquinolinilo quinazolinilo piridilo pirazinilo pirimidilo furanilo pirrolilo tienilo tiazolilo triazinilo oxazolilo isoxazolilo imidazolilo

indolilo benzofuranilo benzotiazolilo tetrahidrofuranilo tetrahidropiranilo pipendinilo morfolinilo piperazinilo y pirrolidinilo Tales grupos heterocíclicos pueden ser adicionalmente sustituidos por ejemplo con hidroxi alquilo alcoxi halógeno y amino

Como se utiliza aquí alquilo está destinado a incluir tanto grupos de hidrocarburos alifáticos ramificados y saturados de cadena recta que tienen el número específico de átomos de carbono Ejemplos de alquilo incluyen pero no están limitados a metilo etilo n propilo i propilo n butilo s-butilo t butilo n pentilo y s-pentilo Los grupos alquilos preferidos son grupos alquilos C_1-C_{10} Los grupos alquilos especialmente preferidos son metilo etilo propilo butilo y 3-pentilo El término alquilo C_{1-4} como se utiliza aquí incluye grupos alquilos que consisten de 1 a 4 átomos de carbono que pueden contener una porción ciclopropilo Ejemplos adecuados son metilo etilo ciclopropilmetilo

El término carbhidnlo se refiere tanto a grupos hidrocarburo de cadena ramificada y recta que son saturados o insaturados En otras palabras un grupo carbhidnlo puede ser alquilo alquenilo o alquinilo El numero de átomos de carbono se puede especificar como se indicó anteriormente

Cicloalquilo está destinado a incluir grupos de anillos saturados que tienen el número especificado de átomos de carbono tal como ciclopropilo ciclobutilo ciclopentilo o ciclohexilo Los grupos cicloalquilo que típicamente tendrán de 3 a 8 miembros por anillo

En el término (cicloalquilo C_3-C_7) alquilo C_1 C_4 cicloalquilo y alquilo son como se definió anteriormente el punto de unión es sobre el grupo alquilo El término

comprende pero no está limitado a ciclopropilmetilo ciclohexilmetilo y ciclohexilmetilo

Alquenilo está destinado a incluir cadenas de hidrocarburos de configuración recta o ramificada que comprenden uno o más uniones carbono-carbono insaturadas que pueden ocurrir en cualquier punto estable a lo largo de la cadena tal como etenilo y propenilo Los grupos alquenilo típicamente tendrán 2 a aproximadamente 8 átomos de carbono más típicamente 2 a aproximadamente 6 átomos de carbono

Alquinilo está destinado a incluir cadenas de hidrocarburos de configuración recta o ramificada que comprenden uno o más triples enlaces de carbono-carbono que pueden ocurrir en cualquier punto estable a lo largo de la cadena tal como etinilo y propinilo Los grupos alquinilos típicamente tendrán 2 a aproximadamente 8 átomos de carbono más típicamente 2 a aproximadamente 6 átomos de carbono

Carbhidnio es independientemente recto ramificado o cíclico que contiene cero o uno o más dobles o triples enlaces

Haloalquilo está destinado a incluir tanto grupos de hidrocarburos alifáticos saturados de cadena ramificada y recta que tienen el numero específico de átomos de carbono sustituidos con uno o más átomos de halógeno Ejemplos de haloalquilo influyen pero no están limitados a mono di o tri-fluorometilo mono- di o tri-clorometilo mono- di- tri tetra o penta fluoroetilo y mono- di tri- tetra o penta-cloroetilo Típicamente los grupos haloalquilo tendrán de 1 a

aproximadamente 8 átomos de carbono más típicamente 1 a aproximadamente 6 átomos de carbono

Alcoxi representa un grupo alquilo como se definió anteriormente con el número indicado de átomos de carbono unido a través de un puente de oxígeno Ejemplos de alcoxi incluyen pero no están limitados a metoxi etoxi n propoxi i propoxi n butoxi 2 butoxi t butoxi n-pentoxi 2-pentoxi 3 pentoxi isopentoxi neopentoxi n hexoxi 2 hexoxi 3 hexoxi y 3 metilpentoxi Los grupos alcoxi típicamente tendrán de 1 a aproximadamente 8 átomos de carbono como más típicamente 1 a aproximadamente 6 átomos de carbono

Haloalcoxi representa un grupo haloalquilo como se definió anteriormente con el numero indicado de átomos de carbono unido a través de un puente de oxígeno

Como se utiliza aquí el término alquiltio incluye aquellos grupos que tienen uno o más enlaces tioeter y preferiblemente de 1 a 8 átomos de carbono más típicamente 1 a aproximadamente 6 átomos de carbono

Como se utiliza aquí el término alquilsulfinilo incluyen aquellos grupos que tienen uno o más grupos de enlaces sulfoxido (SO) típicamente de 1 a aproximadamente 8 átomos de carbono más típicamente 1 a aproximadamente 6 átomos de carbono

Como se utiliza aquí el término alquilsulfonilo incluye aquellos grupos que tienen uno o más grupos de enlace sulfonilo (SO_2) típicamente de 1 a aproximadamente 8 átomos de carbono más típicamente 1 a aproximadamente 6 átomos de carbono

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Como se utiliza aquí el término alquilamino incluye aquellos grupos que tienen uno o más grupos amino primarios secundarios y/o terciarios y típicamente de 1 a aproximadamente 8 átomos de carbono más típicamente 1 a aproximadamente 6 átomos de carbono

Halo o halógeno como se utiliza aquí se refiere a fluor cloro bromo o yodo y contra ion se utiliza para representar especies pequeñas cargadas negativamente tales como cloro bromo hidróxido acetato sulfato y similares

Como se utiliza aquí grupo carbocíclico está destinado a significar cualquier monociclo o biciclo de 3 a 7 miembros o grupo bicíclico o triciclito de 7 a 13 miembros cualquiera de los cuales pueden ser saturados parcialmente insaturado o aromático Además de aquellos ejemplificados en cualquier parte aquí ejemplos de tales carbociclos incluyen pero no están limitados a ciclopropilo ciclobutilo ciclopentilo ciclohexilo cicloheptilo adamantilo ciclooctilo [3 3 0] biciclooctanilo [4 3 0] biciclononanilo [4 4 0] biciclodecanilo [2 2 2] biciclooctanilo fluorenilo fenilo naftilo indanilo y tetrahidronaftilo

Como se utiliza aquí el término grupo heterocíclico está destinado a incluir grupos saturados parcialmente insaturados o insaturados (aromáticos) que tienen 1 a 3 anillos (preferiblemente fusionados) con 3 a aproximadamente 8 miembros por anillo al menos un anillo contiene un átomo seleccionado de N O o S Los heteroátomos de nitrógeno o azufre pueden ser opcionalmente oxidados El término heterocicloalquilo se utiliza para referirse a grupos heterocíclicos saturados que tienen uno o más átomos de anillo no carbono (por ejemplo N O S P Si o similares) y el numero especificado de átomos de carbono

Así un heterocicloalquilo C_{3-9} es un grupo cíclico que tiene entre 3 y 9 átomos de carbono en el anillo y al menos un heteroátomo en el anillo

El anillo heterocíclico puede estar unido a su grupo pendiente en cualquier heteroátomo o átomo de carbono que da como resultado una estructura estable Los anillos heterocíclicos descritos aquí se pueden sustituir sobre un átomo de carbono o de nitrógeno si el compuesto resultante es estable Un nitrógeno en el heterociclo puede ser opcionalmente cuaternarizado Como se utiliza aquí el término sistema heterocíclico aromático pretende influir cualquier sistema de anillo aromático monocíclico de 5 a 7 miembros o bicíclico de 10 a 14 miembros estable que comprende átomos de carbono y de 1 a 4 heteroátomos independientemente seleccionados del grupo que consiste de N O y S se prefiere que el número total de átomos de S y O en el heterociclo aromático no sea más de 2 más preferiblemente no más de 1

Ejemplos de heterociclos incluyen pero no están limitados a aquellos ejemplificados en cualquier parte aquí y además incluyen acridinilo azocinilo benzimidazolilo benzofuranilo benzotiofuranilo benzotiofenilo benzoxazolilo benztiazolilo benztriazolilo benztetrazolilo benzisoxazolilo benzisotiazolilo benzimidazolinilo carbazolilo NH-carbazolilo carbolinilo cromanilo cromenilo cinnolinilo decahidroquinolinilo 2H 6H 1 5 2-ditiazinilo dihidrofuro [2 3 b] tetrahidrofurano furanilo furazanilo imidazolidinilo imidazolinilo imidazolilo 1H indazolilo indolenilo indolinilo indolizinilo indolilo 3H indolilo isobenzofuranilo isocromanilo isoindazolilo isoindolinilo isoindolilo isoquinolinilo isotiazolilo isoxazolilo morfolinilo naftindinilo octahidroisoquinolinilo oxadiazolilo 1 2 3 oxadiazolilo 1 2 4-oxadiazolilo 1 2 5-oxadiazolilo 1 3 4-oxadiazolilo

oxazolidinilo oxazolilo oxazolidinilo pirimidinilo fenantridinilo fenantrolinilo fenazinilo fenotiazinilo fenoxatiinilo fenoxazinilo eftalazinilo piperazinilo piperidinilo teridinilo purinilo piranilo pirazinilo pirazolidinilo pirazolinilo pirazolilo piridazinilo pridooxazol piridoimidazol pridotiazol piridinilo pridil pirimidinilo pirrolidinilo pirrolinilo 2H pirrolilo pirrolilo quinazolinilo quinolinilo 4H-quinolizinilo quinoxalinilo quinuclidinilo tetrahidrofuranilo tetrahidroisoquinolinilo tetrahidroquinolinilo 6H 1 2 5 tiadiazinilo 1 2 3-tiadiazolilo 1 2 4-tiadiazolilo 1 2 5-tiadiazolilo 1 3 4-tiadiazolilo tiantrenilo tiazolilo tienilo tienotiazolilo tienooxazolilo tienoimidazolilo tiofenil triazinilo 1 2 3 triazolilo 1 2 4 triazolilo 1 2 5 triazolilo 1 3 4 triazolilo y xantenilo

Los grupos heterocíclicos preferidos incluyen pero no están limitados a piridinilo pirimidinilo furanilo tienilo pirrolilo pirazolilo pirrolidinilo morfolinilo piperidinilo piperazinilo e imidazolilo También están incluidos anillos fusionados y compuestos spiro que contienen por ejemplo los heterociclos anteriores

Como se utiliza aquí el término arilo carbocíclico incluye grupos que contienen 1 a 3 anillos fusionados o separados y de 6 a 18 átomos por anillo Sin los átomos hetero como miembros del anillo Los grupos arilocarboxílicos especialmente preferidos incluyen fenilo y naftilo que incluye 1 naftilo y 2 naftilo

Como se utiliza aquí sales farmacéuticamente aceptables se refieren a derivados de los compuestos descritos aquí en donde los compuestos padre se modifican al hacer ácido no tóxico o sales básicas de estos y adicionalmente se refieren a solvatos farmacéuticamente aceptables de tales compuestos y tales sales Ejemplos de sales farmacéuticamente aceptables incluyen pero no están limitadas a sales de ácido mineral u orgánico de residuos básicos tales como

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aminas sales alcalinas u orgánicas de residuos ácidos tales como ácidos carboxílicos y similares Las sales farmacéuticamente aceptables incluyen las sales no tóxicas convencionales y las sales de amonio cuaternarias de los compuestos padres formados por ejemplo de ácido inorgánicos u orgánicos no tóxicos Por ejemplo las sales de ácido convencional no tóxicas incluyen aquellas derivadas de ácidos inorgánicos tales como ácido clohidrico bromhidrico sulfúrico sulfamico fosfórico nítrico y similares y las sales preparadas de ácidos orgánicos tales como acético propionico succinico glicolico esteárico láctico málico tartarico cítrico ascórbico pamoico maléfico hidroximaleico fenilacetico glutámico benzoico salicilico mesilico sulfanilico 2-acetoxibenzoico fumarico toluenosulfonico metanesulfonico etano disulfonico oxálico isetionico HOOC (CH_2) COOH donde n es 0-4 y similares Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar de un compuesto padre que contiene una porción básica o ácida mediante métodos químicos convencionales Generalmente tales sales se pueden preparar al hacer reaccionar formas de ácidos libres de estos compuestos con una cantidad estioquiométrica de la base apropiada (tal como hidróxido de Na Ca Mg o K carbonato bicarbonato o similar) o al hacer reaccionar formas de base libre de estos compuestos con una cantidad estioquiométrica de un ácido apropiado Tales reacciones son típicamente llevadas a cabo en agua o en un solvente orgánico o en una mezcla de los dos Generalmente medio no acuosos como el éter acetato de etilo etanol isopropanol o acetonitrilo son los preferidos donde sea practicable Las listas de sales adicionales adecuadas se pueden encontrar por ejemplo en el *Remington s Pharmaceutical Sciences* 17 edición Mack Publishing Company Easton PA p 1418 (1985)

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Prodroga están destinadas a incluir cualquier compuesto que se vuelvan compuestos de Fórmula cuando se administran a sujetos mamíferos por ejemplo luego del procesamiento metabólico de prodroga Ejemplos de prodroga incluyen pero no están limitados a acetato formato y benzoato y derivados de grupos funcionales (tales como grupos alcohol o amina) en los compuestos de Fórmula I

Las combinaciones de los sustituyentes y/o variables son permisibles solamente si tales combinaciones resultan en compuestos estables o en intermedios sintéticos utiles Un compuesto estable o una estructura estable o en intermedio sintéticos útiles Un compuesto estable o una estructura estable significan implicar un compuesto que es suficientemente robusto para sobrevivir el aislamiento de una mezcla de reacción y la subsecuente formulación en un agente terapéutico efectivo El término cantidad terapéuticamente efectiva de un compuesto de esta invención significa una cantidad efectiva cuando se administra a un paciente humano o no humano para suministrar un beneficio terapéutico tal como mejoramiento de síntomas por ejemplo una cantidad efectiva para antagonizar estos efectos de niveles patogénicos de CRF o para tratar los síntomas de desordenes de tensión desorden afectivo ansiedad o depresión

Preparaciones Farmacéuticas

Los compuestos de la Fórmula general I se pueden administrar oralmente tópicamente transdermica parenteralmente mediante inhalación o rociado rectalmente o vaginalmente en formulaciones de dosis unitarias que contienen portadores farmacéuticamente aceptables no tóxicos convencionales adyuvantes y vehículos El término parenteral como se utiliza aquí incluye subcutánea intravenosa intramuscular intratecal subcutánea intravenosa intramuscular

intratecal y tipos similares de inyección o técnicas de infusión Además se suministra una formulación farmacéutica que comprende un compuesto de Fórmula general I y un portador farmacéuticamente aceptable Uno o más compuestos de Fórmula general I pueden estar presentes en asocio con uno o más portadores y/o diluyentes y/o adyuvantes farmacéuticamente aceptables no tóxicos y si se desea otros ingredientes activos Las composiciones farmacéuticas que contienen los compuestos de Fórmula general I pueden estar en una forma adecuada para uso oral por ejemplo como tabletas trociscos pastillas suspensiones acuosas o aceitosas polvo o gránulos dispersables emulsiones cápsulas duras o suaves o jarabe y elíxires

Las composiciones destinadas para uso oral se pueden preparar de acuerdo a cualquier método conocido en la técnica para la elaboración y composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consiste de agentes endulzantes agentes sabonzantes agentes colorantes y agentes preservantes con el fin de suministrar preparaciones farmacéuticamente elegantes y saboreables Las tabletas contienen el ingrediente activo en mezcla con excipientes farmacéuticamente aceptables no tóxicos que son adecuados para la elaboración de las tabletas Estos excipientes pueden ser por ejemplo diluyentes inertes tales como carbonato de calcio carbonato de sodio lactosa fosfato de calcio o fosfato de sodio agentes granulantes y desintegrantes por ejemplo almidón de maíz o ácido algínico agentes de unión por ejemplo almidón gelatina o acacia y agentes lubricantes por ejemplo estearato de magnesio ácido esteárico talco Las tabletas se pueden ser descubiertas o pueden ser recubiertas mediante técnicas conocidas para retrazar la desintegración y absorción el tracto gastrointestinal y de esta manera suministrar una acción sostenida durante un periodo largo Por ejemplo se puede

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emplear un material para retrazo del tiempo tal como gliceril monoestearato o gliceril distestearato Las formulaciones para uso oral también pueden ser presentadas como capsulas de gelatina dura en donde el ingrediente activo está mezclado con diluyente sólido inerte por ejemplo carbonato de calcio fosfato de calcio o caulín o como capsulas de gelatina suave en donde el ingrediente activo se mezcla con agua o un medio aceitoso por ejemplo aceite de maní parafina líquida o aceite de oliva

Las suspensiones acuosas contienen los materiales activos en mezcla con excipientes adecuados para la elaboración de suspensiones acuosas tales excipientes son agentes de suspensión por ejemplo carbocarboximetilcelulosa de sodio metilcelulosa hidropropilmetilcelulosa alginato de sodio polivinilpirrolidona goma tragacanto y goma de acacia agentes dispersantes y humectantes pueden ser fosfaturo de ocurrencia natural por ejemplo lecitina o productos de condensación de oxido de alquileno con ácidos grados por ejemplo estearato de polioxietileno o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga por ejemplo heptadecaetilenooxicetanol o productos de condensación de óxido de etileno con éteres parciales derivados de ácidos grasos y un hexitol tal como polioxietileno sorbitol monooleato o productos de condesanción de óxido de etileno con esteres parciales derivados de ácidos grasos y anhídridos de hexitol por ejemplo polioexietileno sorbitan monooleato Las suspensiones acuosas también pueden contener uno o más preservativos por ejemplo etilo o n propilo p-hidroxibenzoato uno o más agentes colorantes uno o más agentes saborizantes y uno o más agentes endulzantes tales como sucrosa o sacarina

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Las suspensiones aceitosas pueden ser formuladas al suspender los ingredientes activos en un aceite vegetal por ejemplo aceite de araquis aceite de oliva aceite de sésamo o aceite de coco en un aceite mineral tal como parafina líquida Las suspensiones aceitosas pueden contener un agente espesante por ejemplo cera de abejas parafina dura o cetil alcohol Los agentes endulzantes tales como aquellos establecidos anteriormente y los agentes saborizantes se pueden agregar para suministrar preparaciones orales saboreables Estas composiciones se pueden preservar mediante la adición de un antioxidante tal como ácido ascórbico

Los polvos dispersables y los gránulos adecuados para la preparación de una suspensión acuosa mediante la adición de agua suministran el ingrediente activo en mezcla con un agente dispersante o humectante agente de suspensión y uno o más preservativos Los agentes dispersantes o humectantes adecuados y los agentes de suspensión son ejemplificados por aquellos ya mencionados anteriormente Los excipientes adicionales por ejemplo agentes saborizantes o colorantes endulzantes pueden estar presente

Las composiciones farmacéuticas de la invención también pueden estar en la forma de emulsiones de aceite en agua La fase aceitosa puede ser un aceite vegetal por ejemplo aceite de oliva o aceite de araquis o un aceite mineral por ejemplo parafina líquida o mezclas de estos Los agentes emulsificantes adecuados pueden ser de ocurrencia natural por ejemplo de acacia goma tragacanto fosfaturo de ocurrencia natural por ejemplo fríjol de soya licita ésteres o ésteres parciales derivados de ácidos grasos y hexitol anhidridos por ejemplo monooleato de sorbitan y productos de condensación de dichos ésteres

parciales con óxido de etileno por ejemplo polioxietileno sorbitan monooleato Las emulsiones también pueden contener agentes endulzantes y saborizantes

Las melazas y los elíxires se pueden formular con agentes endulzantes por ejemplo glicerol propilenglicol sorbitol o sucrosa Tales formulaciones también pueden contener un demulcente un preservativo y agentes saborizantes y colorantes Las composiciones farmacéuticas pueden estar en la forma de un a suspensión acuosa u oleaginosa inyectable estéril Esta suspensión se puede formula de acuerdo a la técnica conocida utilizando aquellos agentes de dispersión o humectantes adecuados y agentes de suspensión que han sido ya mencionados La preparación inyectable estéril puede ser una solución inyectable estéril una solución o suspensión inyectable estéril en un diluyente o solvente farmacéuticamente aceptable no tóxico por ejemplo como una solución de 1 3 butanediol Entre los vehículos aceptables y los solventes que se pueden emplear está el agua la solución de Ringer y la solución de cloruro de sodio isotónica Además los aceites estériles fijos son convencionalmente empleados como un solvente o un medio de suspensión Para este propósito cualquier aceite fijo blando se puede emplear incluyendo mono-o diglicéridos sintéticos Además los ácidos grasos tales como ácido oleico encuentran uso en las preparaciones de los inyectables

Los compuestos de Fórmula general I también pueden ser administrados en forma de supositorios por ejemplo para administración rectal de la droga Estas composiciones se pueden preparar al mezclar la droga con un excipiente no irritante adecuado que sea sólido a temperatura ordinaria pero líquido a temperatura del cuerpo y por lo tanto se fundirá en el cuerpo par liberar la droga Tales materiales incluyen manteca de cacao y polietilenglicoles

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Los compuestos de Fórmula general I pueden administrar parenteralmente en un medio estéril La droga dependiendo del vehículo de la concentración utilizada pueden ser suspendidas o disueltas en el vehículo Ventajosamente uno o más adyuvantes tales como preservativos agentes amortiguantes o anestésicos locales pueden estar presentes en vehículo

Los niveles de dosis del orden de desde aproximadamente 0 05 mg a aproximadamente 100 mg por kilogramo de peso de cuerpo por día son utiles para el tratamiento de las condiciones anteriormente indicadas los rangos de dosis preferidas de aproximadamente 0 1 a aproximadamente 30 mg por kg y más preferiblemente 0 5 a aproximadamente 5 mg por kg por sujeto por día La cantidad de ingrediente activo se puede combinar con los materiales portadores para producir una forma de dosis simple variedad dependiendo del huésped tratado y del modo particular de administración Las formas de dosis unitarias contendrán generalmente desde aproximadamente 0 1 mg a aproximadamente 750 mg de un ingrediente activo

La frecuencia de dosis también puede variar dependiendo del compuesto utilizado y de la enfermedad particular tratada Sin embargo para el tratamiento de la mayoría de desordenes de CNS y gastrointestinales un régimen de dosis de 4 veces diariamente preferiblemente 3 veces diariamente más preferiblemente 2 veces diariamente y más preferiblemente 1 vez diariamente se contemplan Para el tratamiento de tensión y depresión un régimen de dosis de uno a dos veces diariamente es particularmente preferido

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Se entenderá sin embargo que el nivel de dosis específico para cualquier paciente particular dependerá de una variedad de factores que incluye la actividad del compuesto específico empleado la edad el peso del cuerpo la salud general el sexo la dieta el tiempo de administración la ruta de administración y la proporción de excreción la combinación de droga (es decir otras drogas que son utilizadas para tratar el paciente) y la severidad de la enfermedad particular sometidas a terapia

Los compuestos preferidos de la invención tendrán ciertas propiedades farmacológicas Tales propiedades incluyen pero no están limitadas a biodisponibilidad oral de tal forma que la formas de dosis oral preferidas discutidas anteriormente pueden suministrar niveles terapéuticamente efectivos del compuesto in vivo La penetración de la barrera del cerebro a la sangre es necesaria para la mayoría de los compuestos utilizados para tratar desordenes CNS aunque niveles bajos en el cerebro de compuestos utilizados para tratar desordenes periféricos son generalmente los preferidos

Se pueden utilizar ensayos para predecir estas propiedades farmacológicas deseadas Los ensayos utilizados para predecir la biodisponibilidad incluyen transporte a través de mono capas de célula de intestinos humanos que incluyen mono capas de célula Caco-2 La toxicidad a hepatocitos cultivados se puede utilizar para predecir la toxicidad del compuesto siendo los compuestos no tóxicos preferidos La penetración de la barrera del cerebro a la sangre de un compuesto en humanos se puede predecir de los niveles en el cerebro de los compuestos en los animales de laboratorio dado el compuesto por ejemplo intravenosamente

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El porcentaje de unión de proteína de suero se puede predecir de ensayos de unión de albúmina Ejemplos de tales ensayos son descritos en una revisión de Oravcova et al (Journal de Cromatography B (1996) volume 677 pages 1 27) Los compuestos preferidos exhiben unión de proteína de suero reversible preferiblemente esta unión es de menos de 99% más preferiblemente menos de 95% aún más preferiblemente menos del 90% y más preferiblemente del 80%

La frecuencia de administración es generalmente inversamente proporcional a la vida media *in vivo* de un compuesto La vida media *in vivo* de compuestos se pueden predecir de ensayos *in vitro* de vidas media microsomales como se describe Kuhnz y Gieschen (Drug Metabolism y Disposition (1998) volume 26 pages 1120 1127) Las vidas medias preferidas son aquellas que permiten una frecuencia preferida de administración

Como se discutió anteriormente los compuestos preferidos de la invención exhiben una actividad ensayos de unión de receptor CFR *in Vitro* estándar preferiblemente el ensayo como se especificó en el ejemplo 51 que sigue La referencia aquí a ensayo de unión de receptor *in Vitro* estándar" está destinada a referirse a protocolo de ensayo estándar tales como lo protocolos definidos en el Ejemplo 51 que sigue Los compuestos generalmente preferidos de la invención tienen un IC_{50} (concentración inhibitoria máxima media) de aproximadamente 1 micromolar o menos aún más preferiblemente un IC_{50} de aproximadamente 100 nanomolar o menos aún más preferiblemente un IC_{50} de aproximadamente 10 nanomolar o menos en tales ensayos de unión de receptores CRF *in Vitro* estándar definidos como se ejemplifican por el Ejemplo 51 que sigue

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EJEMPLOS

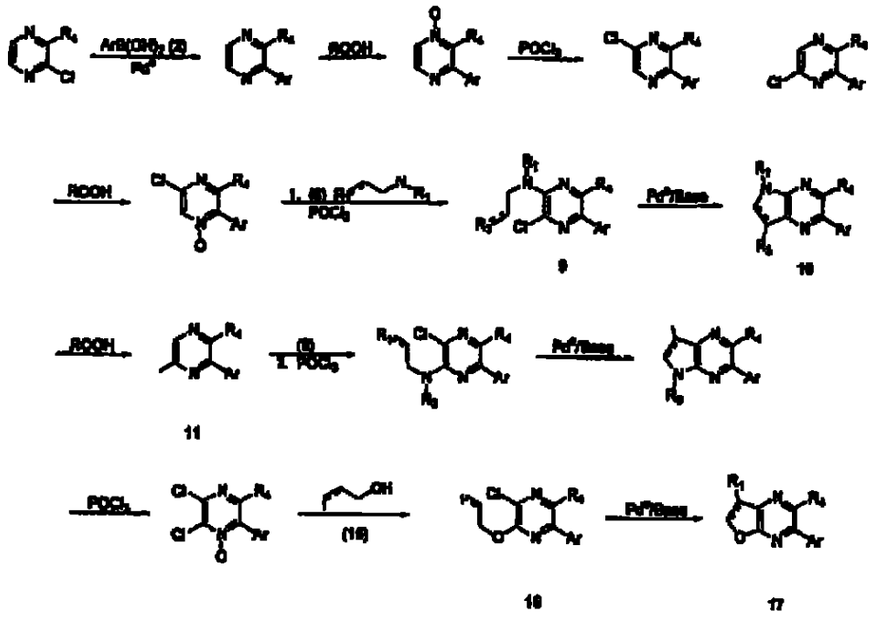
Preparación de Compuestos

Los compuestos de la presente invención se pueden preparar en un número de formas bien conocidas por aquellos expertos en la técnica de síntesis orgánica Los compuestos de la presente invención se pueden sintetizar utilizando los métodos descritos adelante junto con los métodos sintéticos conocidos en la técnica de química orgánica sintética o variaciones sobre estas como se aprecian por aquellos expertos en el arte Los métodos preferidos incluyen pero no están limitados aquellos métodos descritos adelante Cada una de las referencias citadas adelante se incorpora aquí como referencia Los métodos preferidos para la preparación de los compuestos de la presente invención incluyen pero no están limitados a aquellos descritos en el esquema 1 Aquellos que son expertos en la técnica reconocerán que los materiales de partida se pueden variar y las etapas adicionales empleadas para producir los compuestos comprendidos por la presente invención

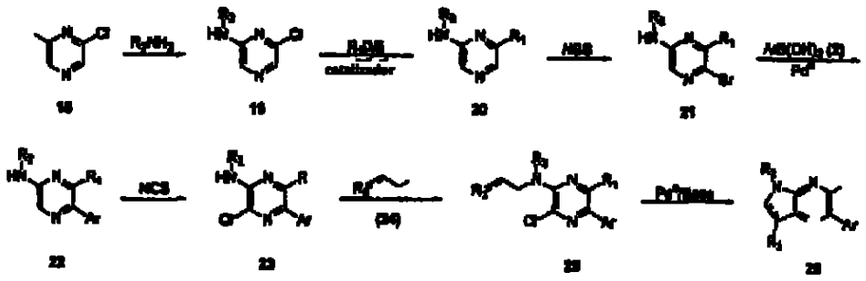
Esquema I

Síntesis de Pirrolo[2 3 b]pirazinas y Furo [2 3 b] pirazinas

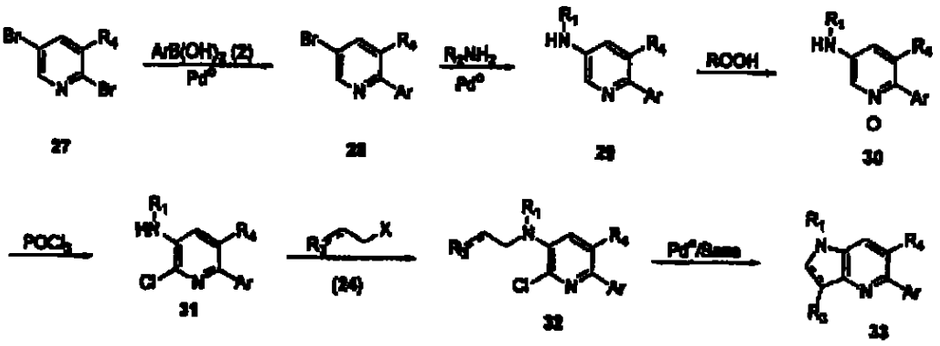
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Esquema II

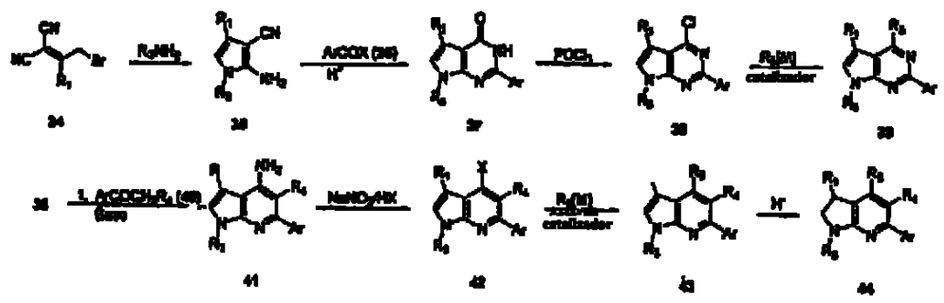


Esquema III

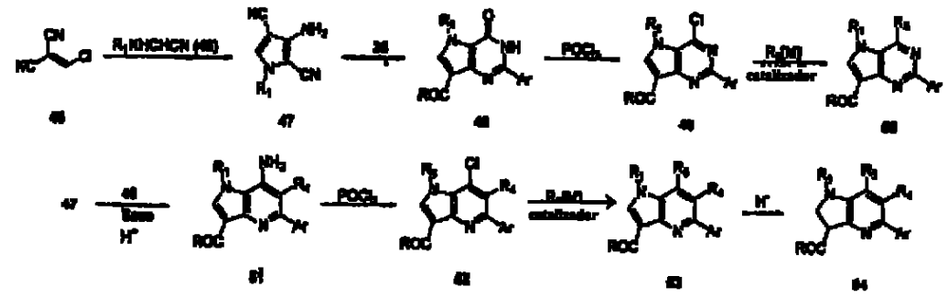


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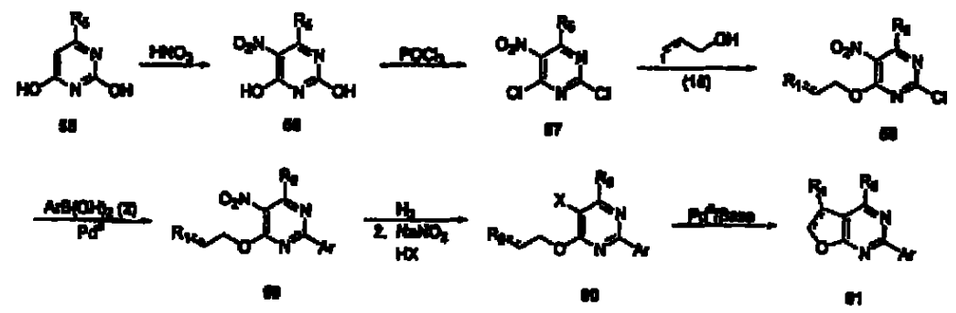
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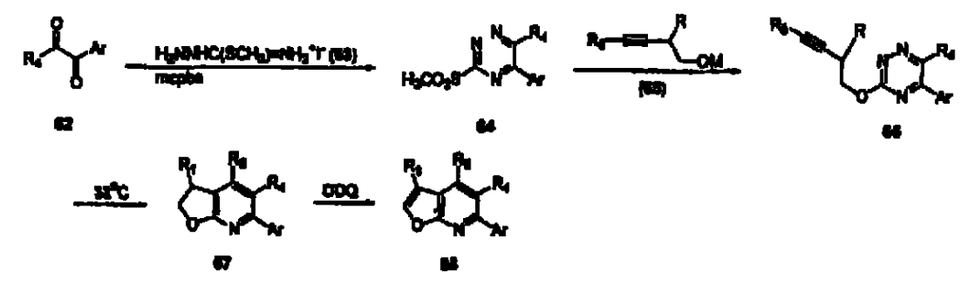
Esquema V



Esquema VI



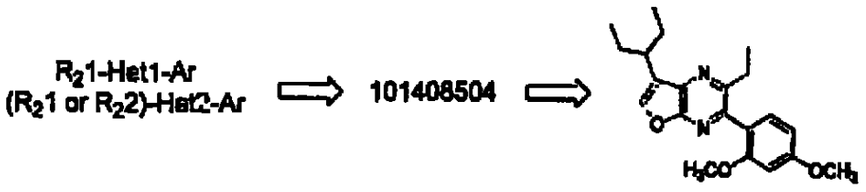
Esquema VII



Compuestos Ejemplificados de la Invención

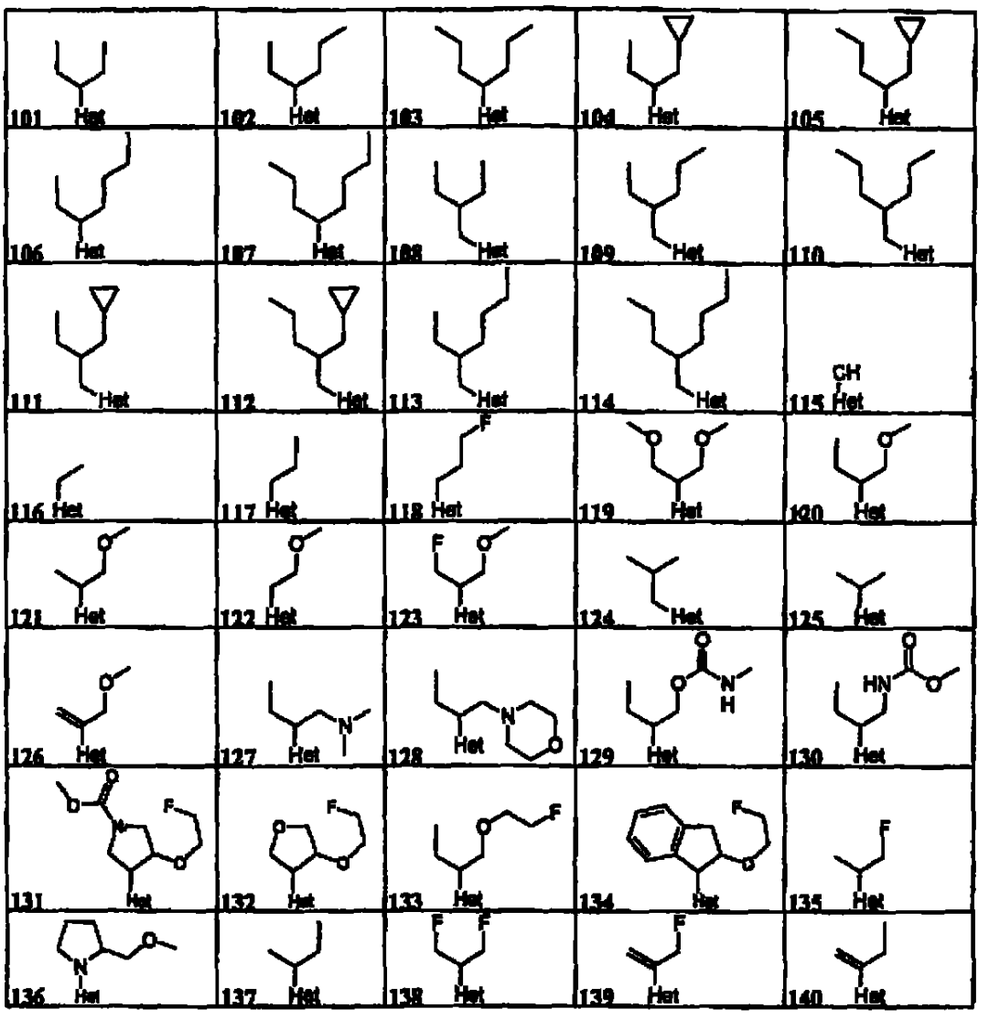
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Las tablas de la matriz R_21 la matriz R_22 la matriz Het y la matriz Ar adelante establecen un número de compuestos de la invención que son preparados mediante los métodos ilustrados en los Esquemas de Reacción I VII mostrados anteriormente Los compuestos se forman al combinar cualquier elemento de la matriz R_21 o la matriz R_22 con cualquier elemento de la matriz Het para formar una porción R_21 Het o R_22 y luego combinar esa porción con cualquier elemento de la matriz Ar para formar un compuesto de la invención Por ejemplo la combinación del elemento 101 de la matriz R_21 con el elemeneto 408 de la matriz Het da la porción 101408 Esta porción es luego combinada con el elemento 504 de la matriz Ar para formar un compuesto de la invención el compuesto 101408504 el cual es 3 (2 4-Dimetoxi fenil) 2-etil 7 (1-etil propil) furo[2 3-b] pirazina

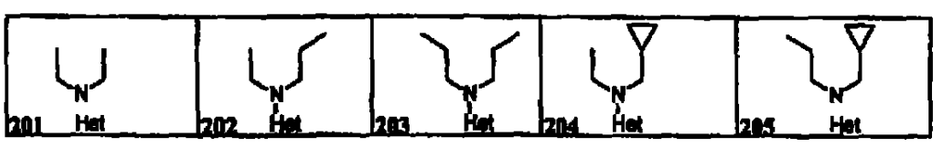


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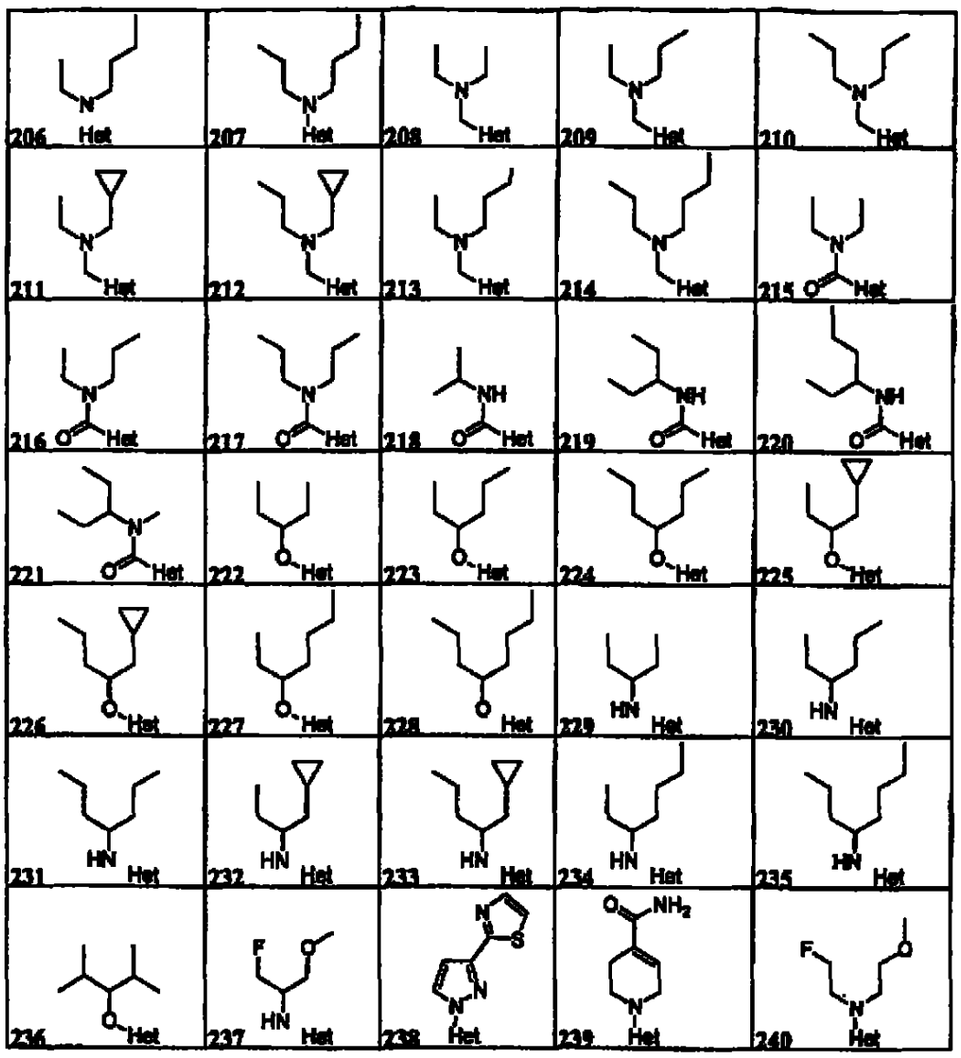
Matriz R_21



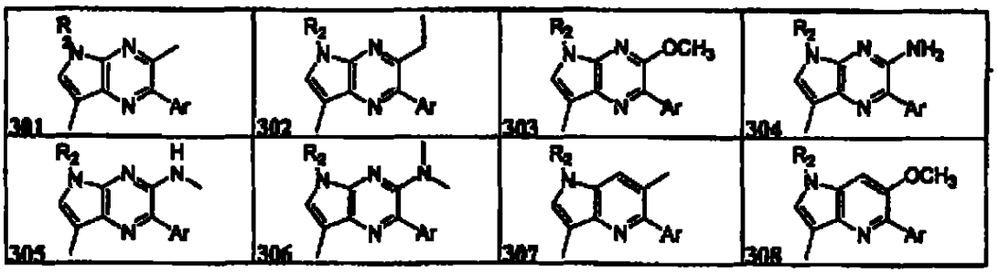
Matrız R_22



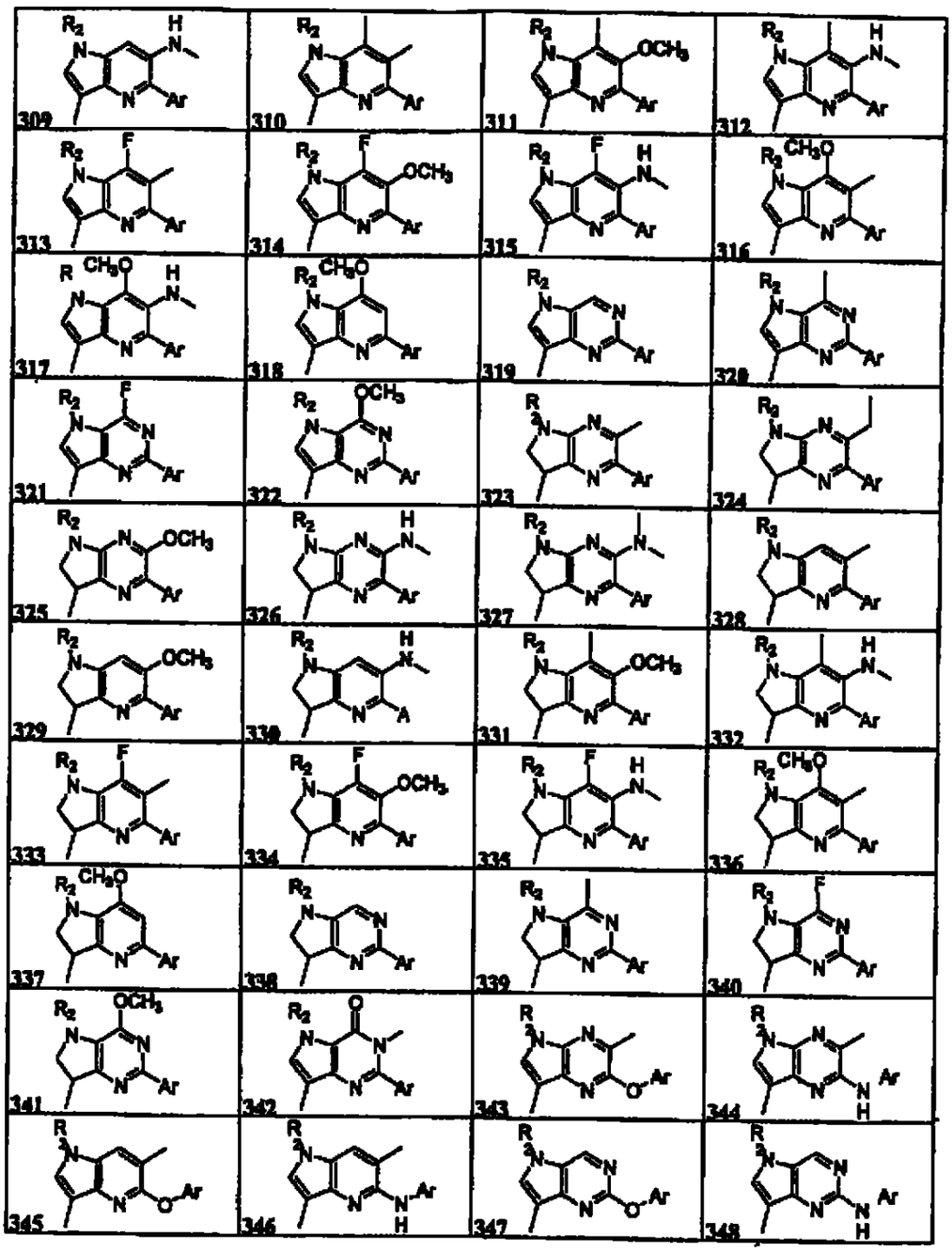
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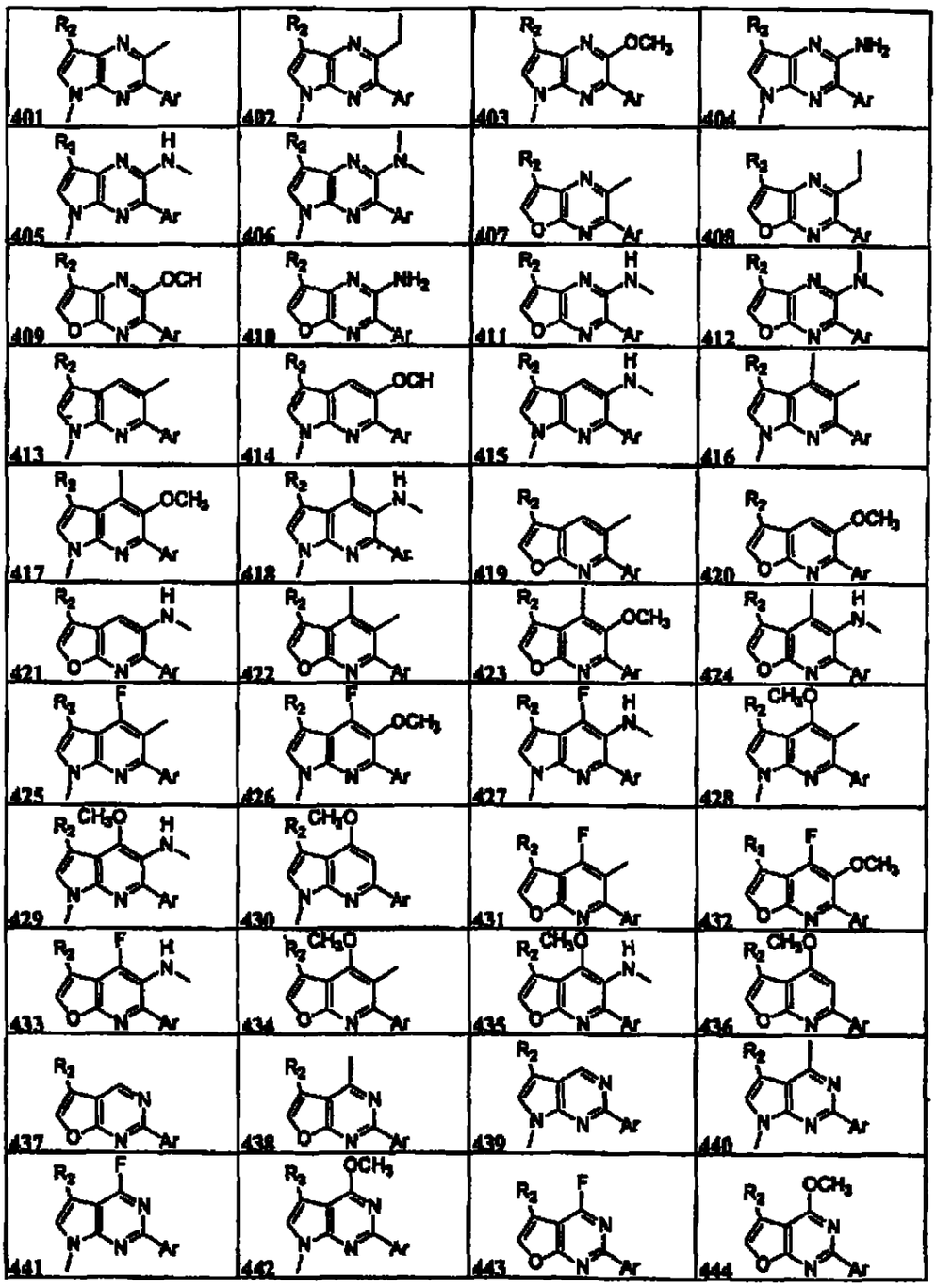
Matrız Het1



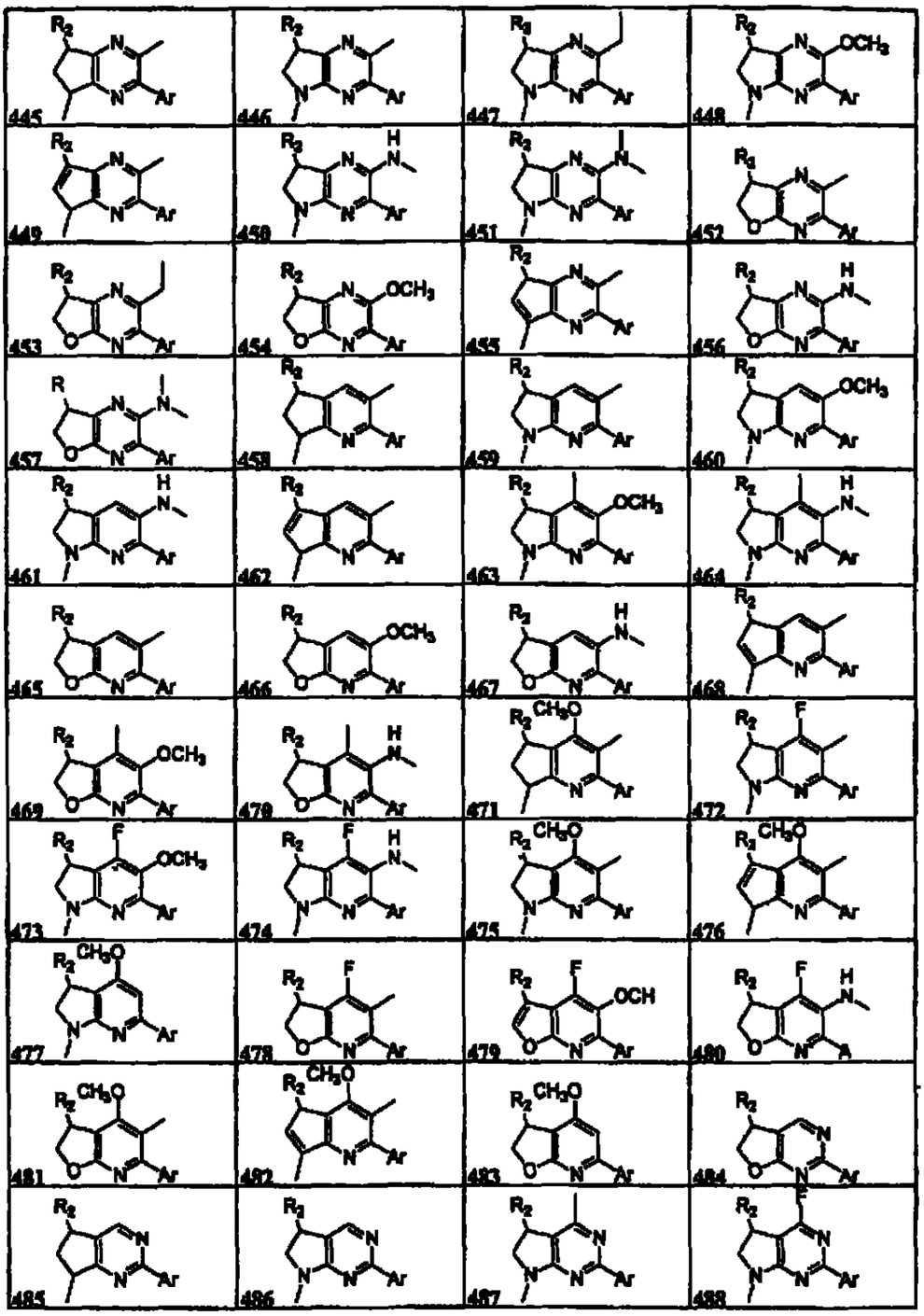
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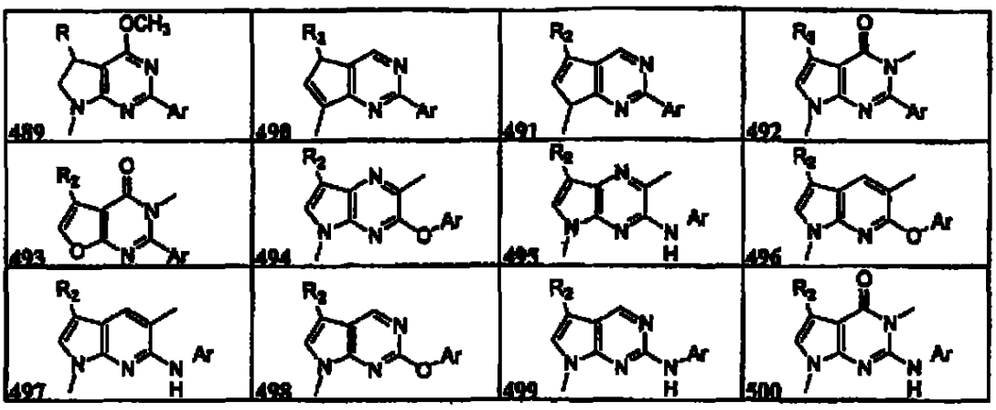
Matriz Het2


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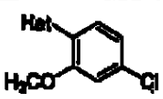
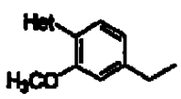
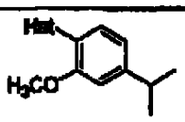
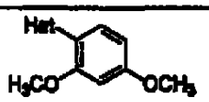
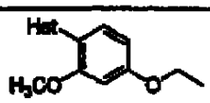
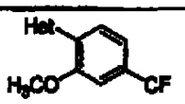
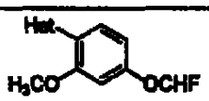
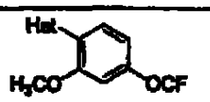
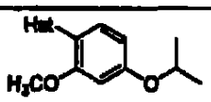
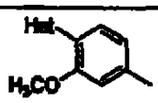
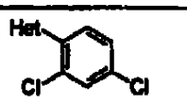
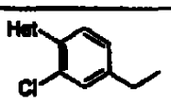
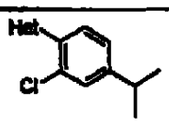
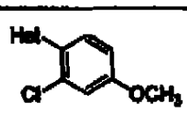
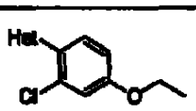
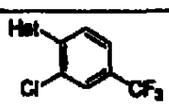
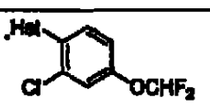
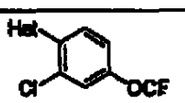
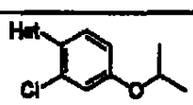
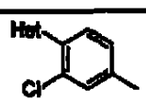
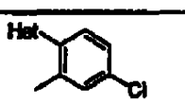
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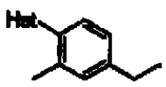
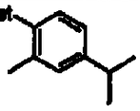
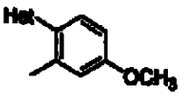
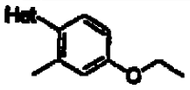
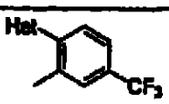
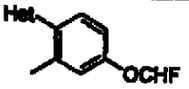
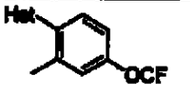
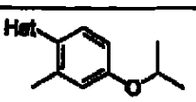
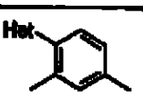
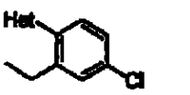
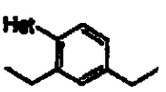
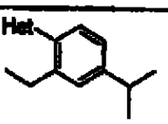
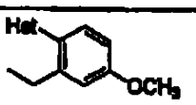
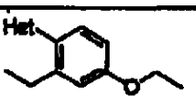
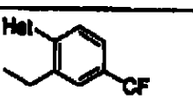
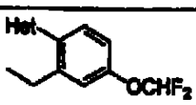
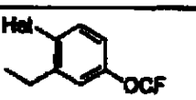
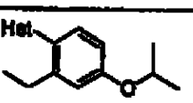
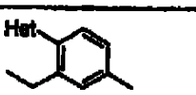
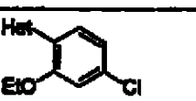
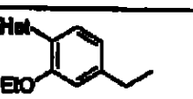
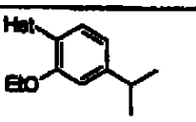
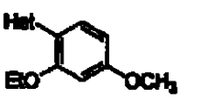
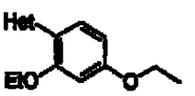
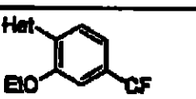
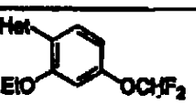
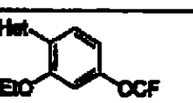
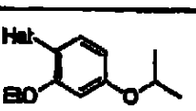
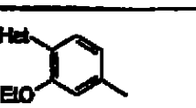
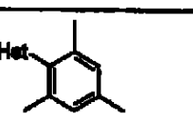
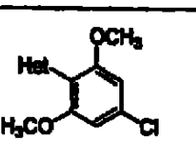
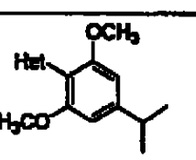
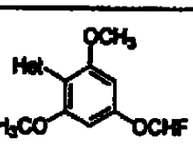
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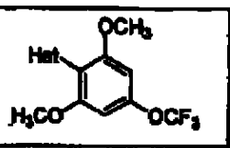
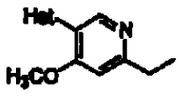
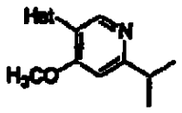
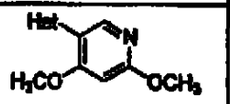
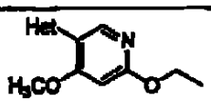
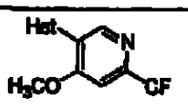
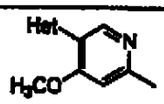
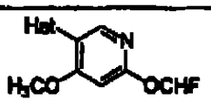
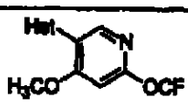
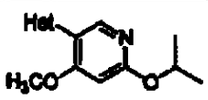
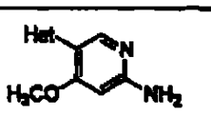
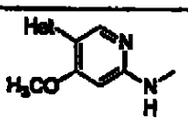
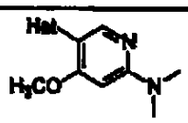
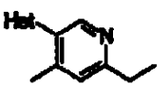
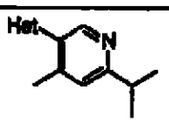
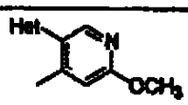
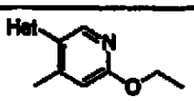
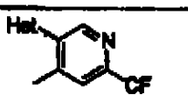
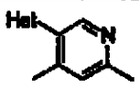
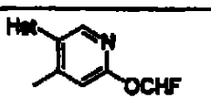
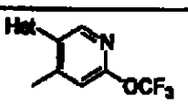
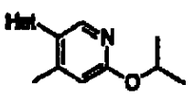
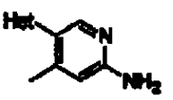
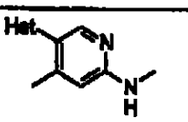
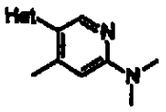
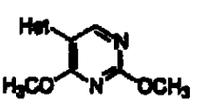
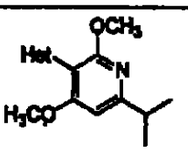
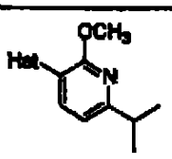
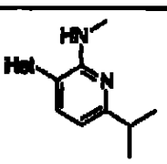
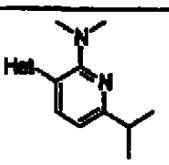
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Todos los compuestos listados adelante se han caracterizado al menos por ^{1}H RMN y LCMS Uno de los siguientes métodos LCMS se utiliza para los compuestos listados adelante

Método 1

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Instrumentación HPLC Los análisis son desarrollados utilizando una bomba serie Waters 600 (Waters Corp) un detector de arreglo de Diodo Waters 996 y un auto-muestrador Gilson 215 (Gilson Inc) Los datos son adquiridos utilizando un software MassLynx 4 0 con un procesamiento OpenLynx

Condiciones HPLC Columna 4 6x50mm XTerra MS C18 5 mm (Waters Corp) espectro UV 10 /seg 220 254nm proporción de flujo 4 0 mL/min volumen de inyección 1 10 µl condiciones de gradiente-fase móvil A 95% agua 5% Metanol con 0 05% de ácido fórmico Fase móvil B 95% metanol 5% agua con 0 025% de ácido fórmico

Gradiente	Time (min)	%B
	0	5
	0 01	5
	1 0	100
	2 0	100
	2 1	5

Instrumentación MS Los experimentos LC MS se desarrollaron utilizando un espectrómetro de masa Waters ZMD II

Condiciones MS La ionización positiva de Electrorociado el voltaje capilar 3 5kV voltaje de cono 30V desolvación y temperatura fuente 250 C y 100 C respectivamente rango de masa 120-800 con un tiempo de exploración de 0 5 segundos y un retrazo interexploración de 0 1 min

Método 2

Condición de Inyección de Flujo

Un sistema de HPLCS Perkin Elmer (bombas series tow 200 micro LC bomba A y bomba B con automuestrador series 200) se utiliza para desarrollar la inyección de flujo La fase móvil es una combinación de 85% metanol (bomba B) con 15% de agua (bomba A) la proporción de flujo es 1 0 mL/min y el volumen de inyección es 3 µL

Instrumentación MS La experimentación LC MS se desarrolla utilizando un espectometro de masas Sciex 150MA

C ndición MS La fuente de ion es un Nebulizador Calentado (ionización química a presión atmosférica) el rango de masa es 100 1000 amu Ambos modos positivo y negativo están en su lugar Para el modo de ion positivo la corriente nebulizadora es 2 0 mA y la temperatura es 350 C El gas nebulizador es 10 y el gas Cortina es 12 El potencial de desagrupaciones 30 V El potencial de enfoque es 200 V y el potencial de entrada es 10 V Para el modo de ion negativo la corriente nebulizadora es 2 0 mA y la temperatura es 350 C El gas nebulizador es 10 y el gas de Cortina es 12 El potencial desagregador 30 V El potencial de enfoque es 200 V y el potencial de entrada es 10 V

Método 3

Instrumentación HPLC BOMBA HP1100 detector HP1100 UV con 220 nm automuestrador HTS/PAL de Tecnología Leap datos adquirido por Micromasa Ma

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Condiciones HPLC Columna Synergi 2U HYDRO RP 20 x 4 0mm proporción de flujo 1 0 mL/min en volumen de inyección 5 µL

Condiciones de gradiente Ácido fórmico 0 1% en acetonitrilo acuoso 10 90% acetonitrilo durante 3 min luego 100% acetonitrilo fin a 5 min

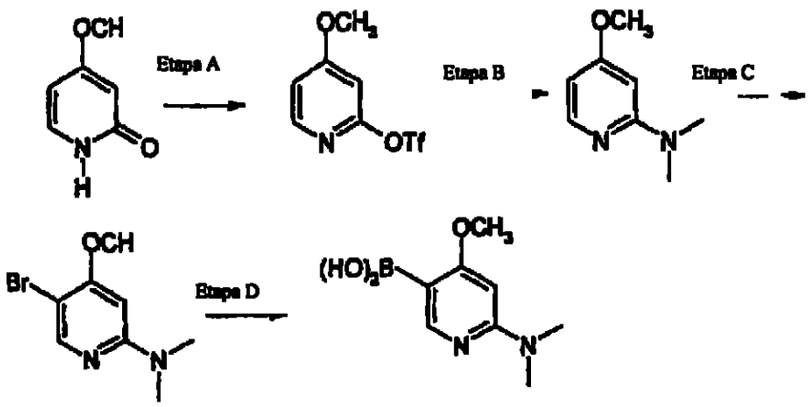
Instrumentación MS Micromasa LCT TOF MS

Condiciones MS Exploración m/z 100 1200 voltaje capilar 3000V voltaje de cono 25V desolvación 200 C y temperatura fuente 100 C

EJEMPLO 1

Preparación de intermedios de ácido borónico

a Síntesis de ácido 2 (dimetilamino)-4 metoxipindin-5-borónico



Etapa A

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A una solución agitada de 4 metoxi 1H pirdin 2-ona (Walters and Shay Tetrahedron Letters 36 (1995) 7575) en cloruro de metileno (30 mL) a 0 C se agrega anhídrido tríflico (12 9 g) seguido por trietilamina (8 4 g) La mezcla de reacción se agita durante 20 min y luego se le permitió calentarse a temperatura ambiente Los componentes volátiles se evaporan bajo vacío y luego el residuo se disuelve en EtOAc y se lava consecutivamente con bicarbonato de sodio acuoso agua y solución salina La fase orgánica se separa se seca y se evapora bajo vacío para dar éster de 4 metoxi pirdin 2 ilo de ácido trifluoro-metanosulfónico Este se utiliza en la siguiente etapa sin purificación adicional

Etapa B

Éster 4-metoxi pirdin 2 ilo ácido trifluoro-metanosulfónico (0 5 g) y dimetilamina (2 4 ml de 2M en THF) se disuelven en DMSO (7 mL) y se calienta durante la noche a 40 C EtOAc se agrega a la mezcla de reacción y esta se lava con solución salina La fase orgánica se separa se seca y se evapora bajo vacío La purificación con gel de sílice da (4-metoxipirdin 2 il) dimetilamina Este se utiliza en la siguiente etapa sin purificación adicional

Etapa C

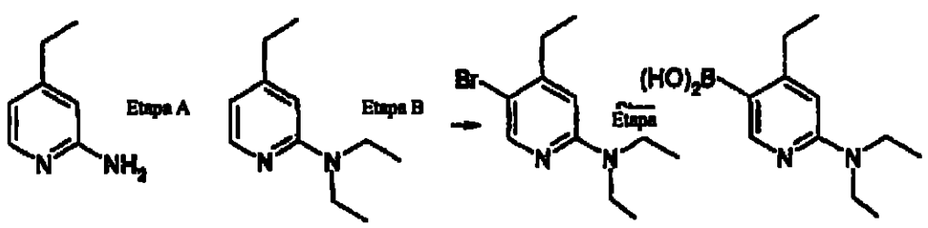
N Bromosuccinimida (1 75 g) se agrega en forma de porciones a una solución de (4 metoxi pirdin 2 il) dimetilamina (1 5 g) a 0 C en cloroformo (30 mL) Después de 30 min se agrega agua (4 mL) a la mezcla de reacción y esta se extrae tres veces con cloruro de metileno La fase orgánica combinada se separa se seca y se evapora bajo vacío La purificación con gel de sílice da (5 bromo-4-metoxi pirdin 2 il) dimetilamina LCMS Rt 1 20 min m/z 231 03 (M+H)

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Etapa D

A una mezcla de n butilitio (2 68 ml de 1 6M en hexanos) y tolueno (7 4 mL) a -65 C se agrega en forma de gotas (5 bromo-4-metoxi pirdin 2 il) dimetilamina (0 9 g) en tolueno (4 mL) La mezcla de reacción se agita en frío durante 30 min y el THF (1 6 mL) se agrega y se continua la agitación durante 15 min Se agrega luego triisopropilborato (1 5 g) lentamente y se continúa la agitación durante 45 min La mezcla de reacción se le permite entonces calentarse a temperatura ambiente durante la noche y se agrega HCl 1N (10 ml) La capa acuosa se separa y la fase orgánica se lava consecutivamente con HCl 1N y agua La fase acuosa combinada se ajusta a pH7 con bicarbonato de sodio sólido y se extrae con 1 1 EtOAc/THF La fase orgánica se separa se seca y se evapora bajo vacío para dar ácido 2 (dimetilamino)-4 metoxipirdin 5-borónico LCMS Rt 2 56 min m/z 197 12 (M+H)

b Síntesis de 2 ácido (dietilamino)-4-etilpirdin-5-borónico



Etapa A

2-Amino-4-etilpiridino (4 70 g) se disuelve en diclorometano (80 mL) Adición de acetaldehido (8 60 mL) y agitación durante 10 min es seguido por adición de triacetoxiborohidruro de sodio (24 6 g) Después de 1h la reacción se pona en una mezcla de agua (300 mL) y bicarbonato de sodio saturado (50 mL) La extracción

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con DCM (3x200 mL) y secado sobre sulfato de magnesio produjo una mezcla cruda que se utiliza en la etapa B sin ninguna purificación adicional LCMS m/z 179 17 (M+H)

Etapa B

La mezcla cruda de la Etapa A se disuelve en cloroformo (150 mL) y enfría a 0 C Adición de NBS (6 50g en tres posiciones) es seguido por agitación durante 15min La solución amarillo claro es luego puesta en una mezcla de agua (500 mL) y bicarbonato de sodio saturado (100 mL) La extracción con DCM (3x150 mL) y secado sobre sulfato de magnesio produjo una mezcla cruda que se purifica sobre gel de sílice LCMS m/z 257 10 (M+H)

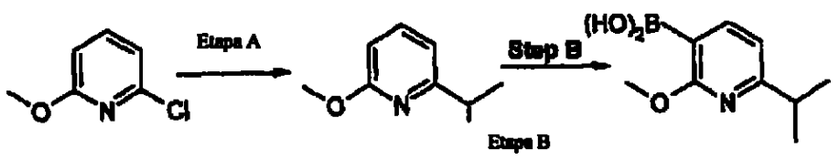
Etapa C

t BuLi (50 1 ml 1 7N en pentanos) se agrega a THF (200 mL) a 78 C Adición lenta del material purificado de la etapa B (7 3 lg en 30 ml de THF) es seguido por agitación durante 15 min a 78 C Luego de revisión LCMS para bromuro sin reaccionar borato de triisopropilo (26 2 mL) se agrega y la mezcla de reacción se calienta a temperatura ambiente durante la noche La solución amarillenta es luego puesta en una mezcla de agua (1000 mL) y bicarbonato de sodio saturado (100 mL) La extracción con DCM (3x300 mL) y secado sobre sulfato de magnesio produjo un material crudo de buena pureza que se puede utilizar en acoplamientos mediados por paladio LCMS m/z 223 19 (M+H)+

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Ácido 2 (Dimetilamino)-4-etilpindin 5 borónico (MS m/z 195 09 (M+H) y ácido 2 (etil metil-amino)-4-etilpindin 5 borónico (MS m/z 209 16 $(M+H)^+$) se preparan análogamente

c Síntesis de ácido 2 isopropil-6-metoxipindino-3 borónico



Etapa A

Siguiendo el procedimiento de Fürstner et al (JACS 124 (2002) 13856) 2-cloro-6-metoxipindino (100 g) se agita a 30 C en una mezcla de THF (2300 mL) y NMP (335 mL) Fe $(acac)_3$ (14 8 g) se agrega seguido por cloruro de magnesio isopropilo (490 ml de 2M en THF) La mezcla de reacción se le permitió calentarse a 0 C durante 1 hora y luego se agrega cloruro de amonio saturado (1000 mL) La fase acuosa se separa y la capa orgánica se lava dos veces con agua (1000 mL) La capa orgánica se destila bajo presión reducida para dar 2 isopropil-6 metoxipindino LCMS Rt 1 95 min m/z 152 12 (M+H)

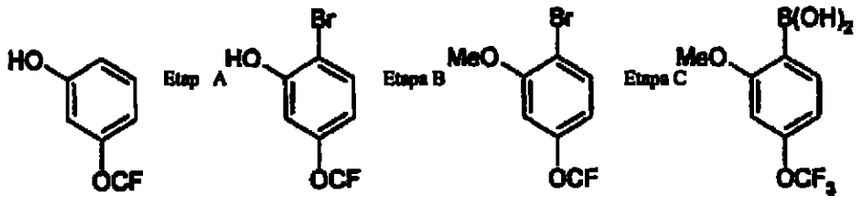
Etapa B

Se disuelven 2 isopropil-6-metoxipindino (191 4 g) y TMEDA (1463 g) en diéter de etilo (1565 mL) y se enfría a -60 C n BuLi (760 ml de 2M) se agrega durante 10 min y la mezcla de reacción se le permitió calentarse a temperatura ambiente durante 3 5 horas La mezcla de reacción se enfría de nuevo a -60 C se agrega trisopropilborato (476 2 g) y se continúa la agitación durante 24 horas 3M HCl se

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agrega luego (510 mL) seguido por agua (2500 mL) La fase acuosa se separa y la capa orgánica se lava tres veces con 5% NaCl acuoso (1500 mL) Las cuatro fases acuosas se extraen secuencialmente con diéter de etilo (2000 mL) y los extractos de éter combinados se concentran bajo vacío para dar ácido 2 isopropil 6 metoxipiridino-3-borónico LCMS Rt 2 80 min m/z 196 11 (M+H)

d Síntesis de ácido 2-metoxi-4 trifluorometoxifenilborónico



Etapa A

3-Trifluorometoxifenol (256 42 g) se disuelve en diclorometano (200 0 mL) y enfría a 5 10 C bajo nitrógeno Se agrega bromo (241 6 g) en forma de gotas durante 2 horas manteniendo la temperatura entre 5-10 C y luego el baño frío se remueve Se agrega agua (1000 mL) y la mezcla se agita durante 10 minutos y se separa Se agrega más agua a la fase orgánica (500 mL) seguido por carbonato de sodio en polvo (10-12 g) hasta que el pH es 10-11 La capa orgánica se separa de nuevo se seca y se concentra bajo vacío La destilación produce 2 bromo 5-trifluorometoxifenol que se utiliza en la siguiente etapa sin purificación adicional

Etapa B

A 2 bromo-5 trifluorometoxifenol (479 g) disuelto en tolueno (2600 mL) a 1 10 C se agrega una solución de hidróxido de sodio (80 g) en agua (400 mL) La mezcla

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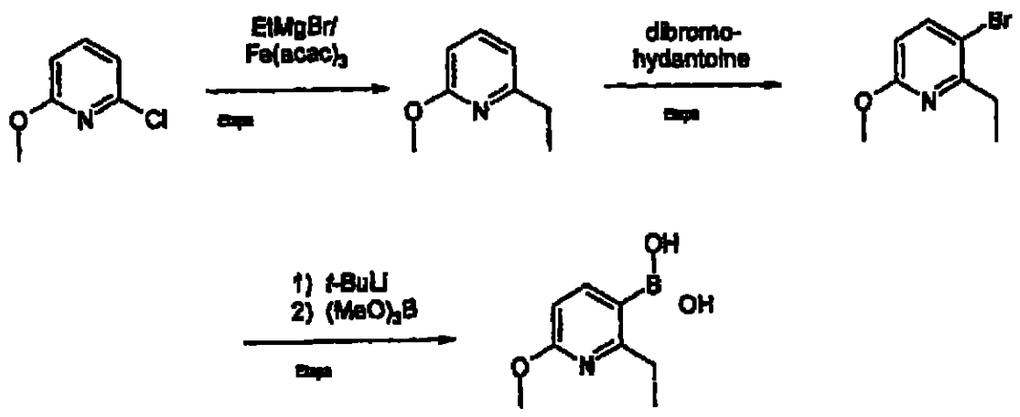
de reacción se agita durante 20 min y luego se agrega bromuro de tetra n butilamonio (24 g) Dimetil sulfato (239 3 g) se divide en cuatro porciones y una porción se agrega a la mezcla cada 30 min manteniendo la temperatura interna cerca de 12 15 C La mezcla de reacción se agita durante la noche a esta temperatura y luego se agrega agua (1000 mL) y la capa orgánica se separa Esta se lava consecutivamente con agua (600 mL) y solución salina (600 mL) y luego se seca y evapora para dar 3-trifluorometoxianisol que se utiliza en la siguiente *etapa sin purificación adicional*

Etapa C

Se agrega n Butilitio (156 ml de 2 5 M solución en hexanos) bajo nitrógeno en THF (800 mL) durante un periodo 5 min mientras mantiene la temperatura entre 77 y 67 C 2 Metoxi-4 trifluorometoxi bromobenceno (100 g) se agrega durante un periodo de 10-min mientras mantiene la temperatura entre 76 0 y -62 C Se agrega Trimetilborato (53 8 g) durante 10 min a temperatura de 76 3 a -63 2 C Después de 1 hora se agrega 200 ml de ácido clorhídrico 2N (200 mL) a pH 1 La mezcla se le permitió calentarse a temperatura ambiente y la fase orgánica se separa y se concentra bajo vacío para dar ácido 2-metoxi-4 trifluorometoxifenilborónico El sólido se trata con n heptano en ebullición para dar ácido 2-metoxi-4 trifluorometoxifenilborónico ^{1}H RMN ($CDCl_3$ 400 MHZ) δ 7 89 (d J = 8 5 Hz 1H) 6 90 (d J=8 5Hz 1H) 6 75 (s 1H) 6 13 (bs 2H) 3 94 (s 3H) Rt 2 87min m/z 281 02 (M+HCOO)

e *Síntesis de ácido 2-etil 6-metoxi-3-pindino borónico*

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Etapa A

El 2-cloro-6 metoxipiridino comercialmente disponible se transforma dentro del compuesto de etilo como se describe correspondientemente durante 2 isopropil-6-metoxipiridino

Etapa B

La mezcla cruda (30 1 g) de la **Etapa B** se disuelve en THF (300 mL) y se trata con 1 3-dibromo-5 5-dimetilhidantoina (1 0-1 2 eq en porciones) Una vez el control TLC muestra conversión completa del material de partida la adición de la hidantoina se detiene y la mezcla se pone en agua (1L) La extracción con DCM (3x300 mL) se seca sobre sulfato de magnesio la purificación sobre gel de sílice produce el bromuro LCMS m/z 215 97 (M+H)

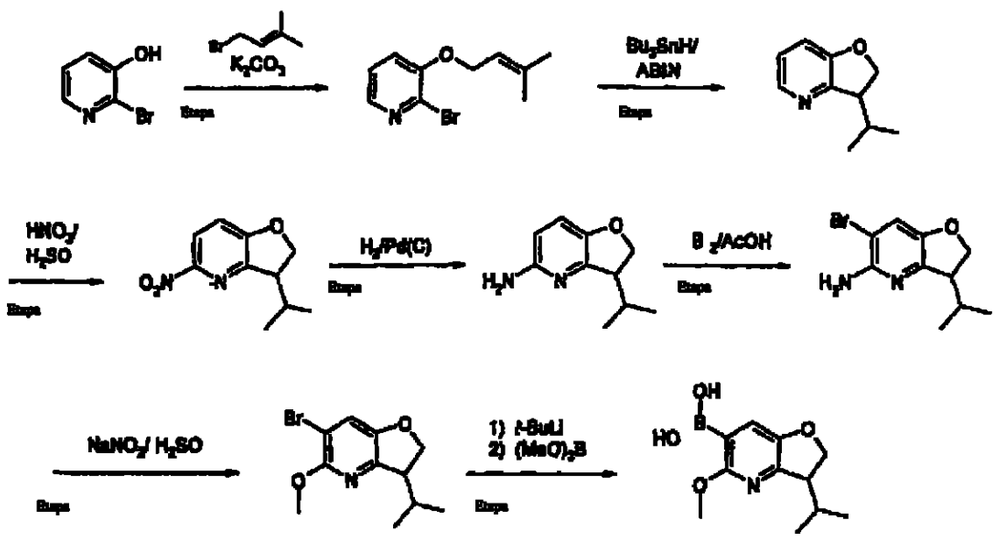
Etapa C

La conversión del bromuro dentro del correspondiente ácido borónico sigue a la ultima etapa de la síntesis previamente descrita de ácido borónico 2-dietilamino-4

2XT

etil-5-piridino con metil borato se usa como electrofilo El material resultante crudo es de buena pureza y se puede utilizar directamente en acoplamientos mediados por paladio LCMS m/z 182 05 (M+H)

f Síntesis de ácido 3-isopropil-5-metoxi-2 3-dihidro-fzcro (3 2-b]pindino 6-borónico



Etapa A

El 2 bromo-3 hidroxipiridino comercialmente disponible (9 41 g) y 3 3 dimetilbromuro de alilo (9 67 g) se disuelven en acetona (150 mL) Después de adición de carbonato de potasio (17 9 g) la mezcla refluye durante 90 min antes de ser puesta en agua (300 mL) La extracción con DCM (4x200 mL) se seca sobre sulfato de magnesio y la purificación sobre gel de sílice produce el éter de alilo LCMS m/z 241 98 (M+H)

Etapa B

246

El éter de la **Etapa A** (960m g) hidruro de tributina (1 28 g) y ABIN (218m g) se disuelven en tolueno (20 mL) y se calienta a 95 C durante 26 h La mezcla resultante se pone en agua (300 mL) y bicarbonato de sodio saturado (30 mL) La extracción con DCM (3x100 mL) se seca sobre sulfato de magnesio y la purificación sobre gel de sílice produjo el bicíclico LCMS m/z 164 13 (M+H)

Etapa C

El éter cíclico (524 mg) de la Etapa B se disuelve en ácido sulfunco conc (5 mL) y luego se enfría a 0 C Después de adición lenta de ácido nítrico gaseoso (1 25 mL) la mezcla de reacción se agita durante 2 h antes de ser puesta en 30 ml de hielo La suspensión resultante se basifica (ph=10) con NaOH 10N y posteriormente se extrae con DCM (3x100 mL) Se seca sobre sulfato de magnesio y la purificación sobre gel de sílice produce el compuesto nitro deseado LCMS m/z 209 14 (M+H)

Etapa D

El compuesto nitro (622 mg) de la Etapa C se disuelve en metanol (20 mL) La reducción se alcanza al añadir una cantidad catalítica de Pd/C (10%) y mantener la atmósfera a un hidrógeno (presión normal) durante 90 min La filtración y concentración a través de celita (10 g) produce una mezcla cruda que es directamente utilizada en la etapa E LCMS m/z 179 11 (M+H)

Etapa E

247

La mezcla cruda de la Etapa D (459 mg) se disuelve en ácido acético (10 mL) y luego se enfría a 0 C para producir una mezcla semi congelada El bromuro (0 139 mL) es lentamente agregado y la reacción se agita durante otros 5 min antes de ser puesta en bicarbonato de sodio saturado (100 mL) y en solución de sulfito de sodio (20 mL) La extracción con DCM (3x100 mL) se seca sobre sulfato de magnesio y la purificación sobre gel de sílice produce el bromuro LCMS m/z 256 98 (M+H)

Etapa F

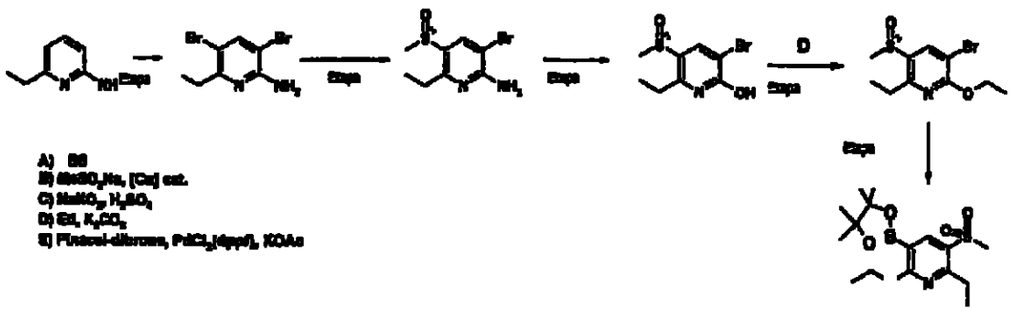
El amino bromuro (500 mg) de la Etapa E se disuelve en una solución de ácido sulfúrico en metanol (10 ml 15% ácido sulfurico) y luego se enfría a 0 C Después de adición de nitrito de sodio (268 mg) a la solución se le permitió calentarse a ta durante un periodo 16 h Después se pone en bicarbonato de sodio sat (100 mL) la capa acuosa se extrajo con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el metoxi bromuro LCMS m/z 272 00 (M+H)

Etapa G

La conversión del bromuro en el correspondiente ácido borónico sigue a la ultima etapa de la síntesis previamente descrita de ácido 2-dietilamino-4-etil 5 pindino borónico con metil borato utilizado como electrofilo El material resultante crudo es de buena pureza y se puede utilizar directamente en acoplamientos mediados por paladio LCMS m/z 238 04 (M+H)

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g *Síntesis de 2-etoxi-6-etil-5-metanosulfonil-3-(4 4 5 5-tetrametil-[1 3 2]dioxaborolan-2-il) pindino*



Etapa A

Una mezcla de 18 8 g de 6-etil pirídin 2 ilamina en 400 ml CH_2Cl_2 se agrega NBS (55 32 g) en forma de porciones a temperatura ambiente Después de adición la mezcla resultante se agita a temperatura ambiente durante 10 min antes se lava con agua y solución salina La fase orgánica resultante se seca se evapora y se purifica por cromatografía de columna (Hexano/EtOAc=7/1) para dar el producto deseado 3 5-dibromo-6-etil pindin 2 ilamina m/z 281 0 (M+H)

Etapa B

3 5-Dibromo-6-etil pindin 2 ilamina (37 5 g) se disuelve en DMSO anhidroso (300 mL) y la mezcla se desgasifica con N_2 durante 2 min seguido por adición de metilsulfonato de sodio (19 5 g) $(CuOTf)_2$ P h H (3 9 g) y trans-1 2-ciclohexano-diamina (3 06 g) Después de agitar a 110 C durante 20 horas la mezcla resultante se diluye con agua se extrae con EtOAc (4x100 mL) se lava con solución salina y se seca sobre Na_2SO_4 Después de evaporación del solvente el residuo se purifica por cromatografía de columna (Hexano/EtOAc=1/1) para dar el

249

producto deseado 3-bromo-6-etil 5-metanosulfonil pirdin 2 ilamina m/z 281 2 (M+H)

Etapa C

3 Bromo-6-etil 5 metanosulfonil pirdin 2 ilamina (7 88 g) se disuelve en H_2SO_4 H_20 (proporción 1 6) (175 mL) y la mezcla se enfría a 0 C Después se agrega la solución de $NaNO_2$ (4 1 g) en 15 ml H_2O en forma de gotas (mantener la temperatura interior por debajo de 5 C) la mezcla se agita a 0 C a temperatura ambiente durante la noche El producto deseado 3 bromo-6-etil-5- metanosulfonil pirdin 2-ol se recolecta por filtración seguido por se lava con agua (50 mL) Este producto crudo se utiliza para la siguiente etapa sin purificación adicional m/z 280 0 (M+H)

Etapa D

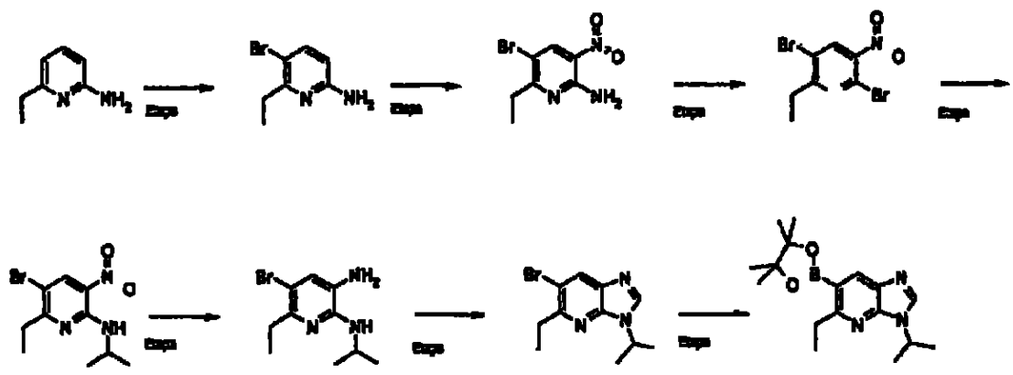
Una mezcla de 3 bromo-6-etil 5-metanosulfonil pirdin 2-ol (15 84 g) y DMF (200 mL) se enfría a 0 C y K_2C0_3 (11 71 g) se agrega seguido por yoduro de etilo (11 3 mL) La mezcla resultante se agita a 0° C a temperatura ambiente durante la noche Después la reacción se completa agua se agrega y la mezcla resultante se extrajo con EtOAc (3x200 mL) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro 3-bromo-2-etoxi-6-etil-5 metanosulfonil pirdino se obtiene después de cromatografía de columna m/z 282 1 (M+H Et)

Etapa E

250

Una mezcla de 3-bromo 2-etoxi-6-etil-5 metanosulfonil pirdino (400 mg) en DMSO (20 mL) se agrega bis (pinacolato) diboron (396 mg) KOAc (382 mg) y $PdCl_2$ (dppf) (49 mg) y la mezcla resultante se agita a 90 C durante la noche Después la reacción se completa la mezcla se vierte en agua y se extrae con acetato de etilo (3x40 mL) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 La purificación por cromatografía flash de columna (Hexano/EtOAc=8/1) da el producto puro 2-etoxi-6-etil-5-metanosulfonil-3 (4 4 5 5-tetrametil-[1 3 2] dioxaborolan 2 il) pirdino m/z 356 3 (M+H)

h Síntesis de 5-etil-3 isopropil-6-(4 4 5 5-tetrametil [1 3 2]dioxaborolan-2 il) 3H imidazo [4 5-b] pirdino



Etapa A

A una solución de 2 amino-6-etil pirdino (50 g) en cloroformo (250 mL) se agrega NBS (73 g) a 0 C durante 30 min La mezcla se agita adicionalmente durante 30 min y se purifica directamente por cromatografía de columna flash sobre gel de sílice para dar 5-bromo-6-etil pirdin 2 ilamina como sólido blanco Rf (hexano EtOAc = 4 1) = 0 34

151
251

Etapa B

Se agrega 5-Bromo-6-etil pirıdın 2 ılamına (34 g) a CH_2SO_4 (110 mL) por debajo de 10 C A la mezcla agıtada se agrega HNO_3 (8 2 mL) por debajo de 15 C durante 40 mın La mezcla se agıta a 0 C durante 1 h a TA durante 1 h y finalmente a 50 C durante 1 h La mezcla se vierte en agua helada y se basıfica por NaOH 50 % Los cristales amarillos se recolectan por filtración son se lavas con agua y secados bajo presión reducida para dar 5-bromo-6-etil 3 nıtro-pırıdın 2 ılamına Rf (hexano EtOAc=4 1) = 0 5

Etapa C

A una suspensión agıtada de 5 bromo-6-etil 3 nıtro-pırıdın 2 ılamına (5 g) en AcOH (20 mL) se agrega HBr 48 % (20 mL) por debajo de 10 C Se agrega bromuro (2 92 mL) a la mezcla por debajo de 10 C durante 15 mın Una solución de $NaNO_2$ a 0 C en agua (3 65 g 15 mL) se agrega durante 20 mın por debajo de 15 C La mezcla se agıta a 0 C durante 30 mın y a TA durante 1 h La mezcla se enfrıa a 0 C neutralizada por 50 % de NaOH y se extrae con DCM El extracto se seca sobre $MgSO_4$ y es concentrado bajo presión reducida para dar 2 5 dıbromo-6-etıl-3-nıtro- pırıdıno como aceite amarillo Rf (hexano EtOAc = 9 1) = 0 7

Etapa D

A una suspensión agıtada de 2 5-dıbromo-6-etıl 3-nıtro pırıdıno (20 g) en EtOH (20 mL) se agrega una solución de ısopropılamına (25 mL) en agua (60 mL) a 0 C La mezcla se agıta a 0 C durante 10 mın y a TA durante 2 h Se forman los cristales

rojo-amarillos recolectados por filtración y se lavan con agua Los cristales humedos se disuelven en DCM (250 mL) Después de secado sobre $MgSO_4$ el solvente se remueve bajo presión reducida para dar (5 bromo-6-etil-3- nitro-pirdin 2 il) isopropil-amina como un sólido rojo-amarillo Rf (hexano EtOAc = 9 1) = 0 77

Etapa E

A una solución de (5-bromo-6-etil 3 nitro-pirdin 2 il)-isopropil-amina (1 g) en EtOH (4 mL) se agrega HCl conc (0 05 mL) agua (1 mL) y hierro reducido (3 g) a ta La mezcla se refluye durante 90 min El residuo de hierro se remueve por filtración y se lava con EtOH El filtrado combinado es concentrado bajo presión reducida Al residuo se agrega agua y la mezcla se extrajo con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ El solvente se remueve bajo presión reducida para dar 5 bromo-6-etil N 2 isopropil pirdino-2 3 diamina como goma LCMS Rt 1 20 min m/z 258 05/260 04 (M+H)

Etapa F

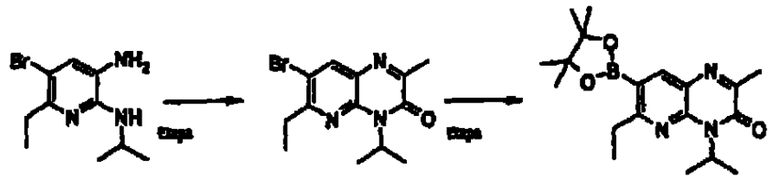
5 Bromo-6-etil N 2 isopropil piridino-2 3-diamina (1 g) se disuelve en dietoximetilacetato (4 mL) y se calienta a 120 C durante 90 min Luego se enfria a TA la mezcla se purifica directamente por cromatografia de columna flash sobre gel de sílice para dar 6-bromo-5-etil-3-isopropil 3H imidazo [4 5 b] pirdino como aceite incoloro Rf (hexano EtOAc = 2 1) = 0 32

Etapa G

253

A una solución de 6-bromo-5-etil 3 isopropil 3H imidazo [4 5-b] pirídino (59 mg) en DMSO (2 mL) se agrega bis (pinacolatoco) diborano (69 mg) KOAc (65 mg) y $PdCl_2$ (dppf) complejo DCM (9 mg) a ta La mezcla se agita a 90 C durante 20 h para dar 5-etil 3-isopropil-6-(4 4 5 5 tetrametil [1 3 2] dioxaborolan 2 il) 3H imidazo [4 5 b] pirídino el cual es capaz de ser utilizado durante el acoplamiento LCMS Rt 1 66 min m/z 316 22 (M+H)

I Síntesis de 6-Etil-4-isopropil-2 metil-7 (4 4 5 5-tetrametil-[1 3 2]dioxaborolan-2 i) 4H-pindo[2 3-b]pirazin 3-ona



Etapa A

A una solución de 5-bromo-6-etil N*2 isopropil pirídino-2 3-diamina (2 38 g) en tolueno (10 mL) se agrega piruvato de etilo (2 05 mL) a ta La mezcla se refluye durante 18 h y se vierte en agua y se extrae con EtOAc El extracto se lava con solución salina y se seca sobre $MgSO_4$ Después de remoción del solvente bajo presión reducida el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar 7 bromo-6-etil-4-isopropil 2 metil- 4H-pindo [2 3-b] pirazin 3 ona como cristal blanco LCMS Rt 1 74 min m/z 310 02/312 02 (M+H)

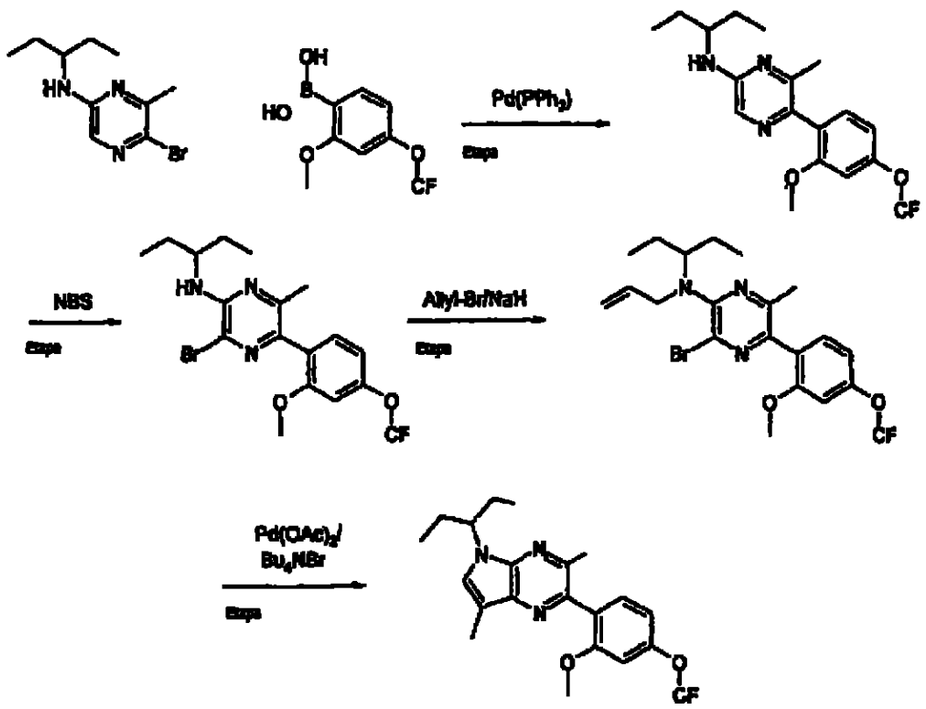
Etapa B

254

A una solución de 7 bromo-6-etil-4 isopropil-2 metil-4H pirido [2 3-b] pirazin 3-ona (0 2 g) en DMSO (4 mL) se agrega bis (pinacolato) diborano (0 2 g) KOAc (0 19 g) y PdC_2 (dppf)-Complejo DCM (29 mg) a ta La mezcla se agita a 90 C durante 20 h para dar 6-etil-4 isopropil 2 metil-7 (4 4 5 5 tetrametil [1 3 2] dioxaborolan 2 il) 4H pirido [2 3 b] pirazin 3-ona que es capaz de ser utilizada durante el acoplamiento LCMS Rt 1 80 min m/z 358 22 (M+H)

EJEMPLO 2

Síntesis de 5-(1-etil-propil) 2-(2-metoxi-4-trifluorometoxi fenil)-3 7-dimetil 5H pirrolo[2 3-b]pirazina



Etapa A

155

El 2 bromo-3 metil 5-isopentilaminopirazina (870 mg) previamente descrito y la literatura conocida ácido 2 metoxi-4 trifluorometoxifenil borónico (796 mg) se disuelven en DME (I5 mL) Después de desgasificar tetrakis (trifenilfosfina) paladio (0) (390 mg) se agrega Una segunda desgasificación es seguida por adición de una solución de carbonato de sodio 1N (6 74 mL) con lo cual la reacción se calienta a 80 C durante 6 h La mezcla amarillenta se coloca entonces en agua (200 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el producto acoplado LCMS m/z 370 17 (M+H)

Etapa B

El producto (205 mg) de la Etapa A se disuelve en cloroformo (10 mL) y se agrega NBS (99 mg) Después de agitarse durante 10 min la mezcla amarillenta se pone en agua (100 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el bromuro LCMS m/z 448 11 (M+H)

Etapa C

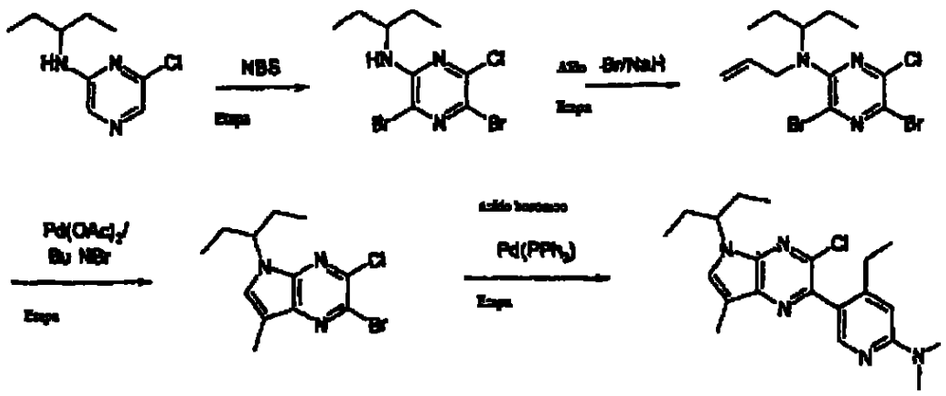
El bromuro (173 mg) de la **Etapa B** y bromuro de alilo (0 33 mL) se disuelven en DMF (5 mL) Se agrega hidruro de sodio (100 mg) y la reacción se agita durante 10 min a ta La mezcla se coloca entonces en agua (100 mL) y se extrae con éter de etilo (2x100 mL) Las capas orgánicas combinadas se lavan con agua (50 mL) se secan sobre sulfato de magnesio y se purifican sobre gel de sílice para producir el compuesto amino alilatado LCMS m/z 488 11 (M+H)

Etapa D

El compuesto alilo (138 mg) de la Etapa C bromuro de tetrabutilamonio (9l mg) acetato de paladio (6 4 mg) y carbonato de potasio (117 mg) se disuelven en DMF (5 mL) Después de calentar a 80 C durante 90 min la mezcla se trabaja de acuerdo con la Etapa C Finalmente la purificación sobre gel de sílice produce el compuesto del título LCMS m/z 408 21 (M+H)

EJEMPLO 3

Síntesis de {5 [3-cloro (1-etil-propil) 7 metil-5H pirrolo[2 3 b]pirazin 2-il-4 etil-piridin 2-il}-dimetil-amin



Etapa A

El 2-cloro-6 isopentilaminopirazina (25 1 g) previamente descrito se disuelve en cloroformo (450 mL) y NBS (47 1 g) se agrega en porciones Después de agitarse durante 30 min la mezcla amarillenta se pone en agua (400 mL) y bicarbonato de sodio saturado (100 mL) se extrae con DCM (3x200 mL) y se seca sobre sulfato

de magnesio El material crudo se lleva a la **Etapa B** sin ninguna purificación adicional Rf = 0 57 en hex/acetato de etilo (10/1)

Etapa B

El material crudo (28 37 g) de la Etapa **A** y bromuro de alilo (20 6 mL) se disuelven en DMF (200 mL) Se agrega hidruro de sodio (4 76 g) en porciones y la reacción se agita durante 5 h a ta La mezcla se coloca entonces en agua (500 mL) y se extrae con acetato de etilo/hexano (1/20 3x300 mL) Las capas orgánicas combinadas se secan sobre sulfato de magnesio y se purifican sobre gel de sílice para producir el producto alilatado LCMS m/z 395 85 (M+H)

Etapa C

El compuesto alilo (23 36 g) de la Etapa **B** bromuro de tetrabutilamonio (19 00 g) acetato de paladio (1 32 g) y carbonato de potasio (24 8 g) se disuelven en DMF (200 mL) Después de calentar a 80 C durante 20 min la mezcla se pone en agua (500 mL) y se extrae con acetato de etilo/hexano (1/4 3x300 mL) Las capas orgánicas combinadas se lavan con agua (100 mL) se secan sobre sulfato de magnesio y se purifican sobre gel de sílice para producir el producto Heck LCMS m/z 316 01 (M+H)

Etapa D

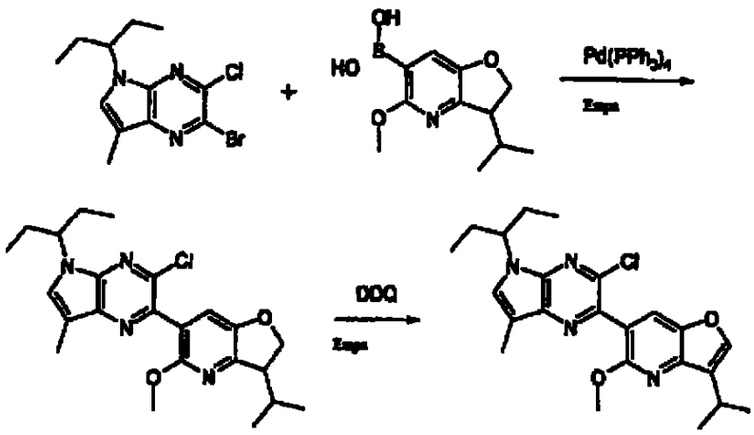
El producto Heck de la Etapa **C** (1 5 g) y el ácido 2-dimetilamino-4-etil 5- pirdino borónico previamente descrito (1 38 g) se disuelven en DME (30 mL) Después de desgasificar se agrega tetrakis (trifenilfosfina) paladio (0) (550 mg) Una segunda

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desgasificación es seguida por adición de una solución de carbonato de sodio 1N (9 5 mL) con lo cual la reacción se calienta a 80 C durante 16 h La mezcla amarillenta se coloca entonces en agua (200 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 386 20 (M+H)

EJEMPLO 4

Síntesis de 3-cloro-5-(1-etil propil) 2-(3-isopropil-5-metoxi furo [3 2-b]piridin 6-il) 7-metil-5H pirrolo[2 3 b]pirazina



Etapa A

El bromuro previamente descrito (85 mg) y el ácido pindino borónico también previamente descrito (64 mg) se disuelven en DME (3 mL) Después de desgasificar se agrega tetrakis (trifenilfosfina) paladio (0) (31 mg) Una segunda desgasificación es seguida por adición de una solución de carbonato de sodio 1N (0 54 mL) con lo cual la reacción se calienta a 80 C durante 16 h La mezcla amarillenta se coloca entonces en agua (100 mL) se extrae con DCM (3x100 mL)

y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el producto acoplado LCMS m/z 429 08 (M+H)

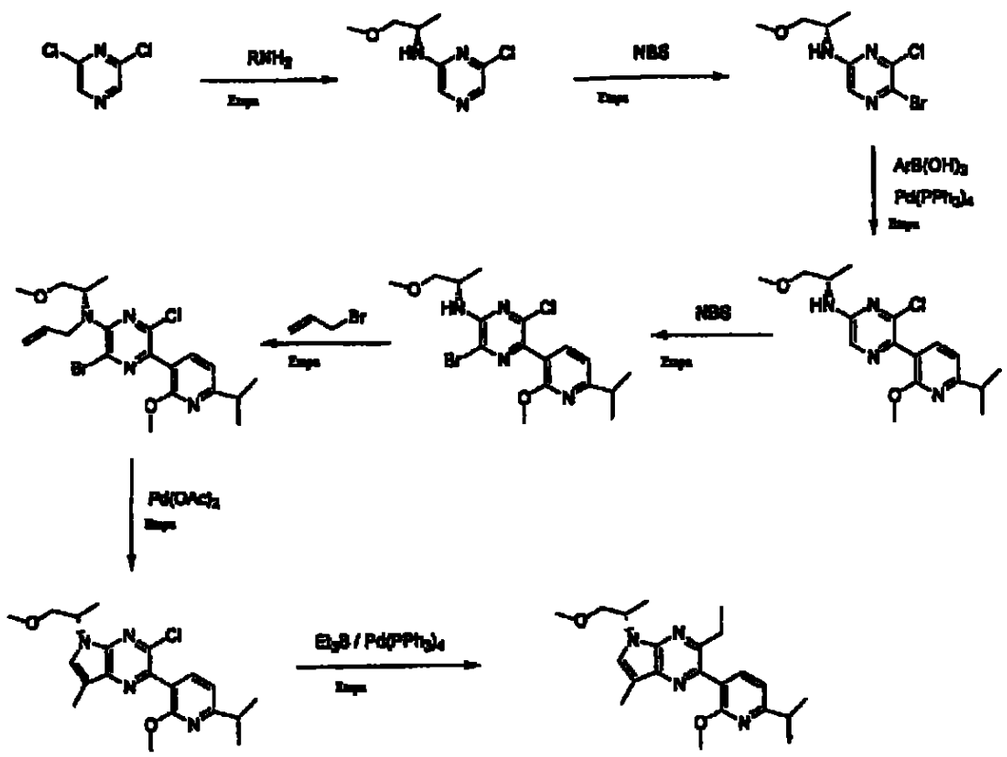
Etapa B

El producto Suzuki (52 mg) de la Etapa A y DDQ (41 mg) se disuelven en benceno (5 mL) y se calienta a 80 C durante 3 h La mezcla de reacción se coloca entonces en agua (100 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 427 12 (M+H)

EJEMPLO 5

Síntesis de (S)-3-cloro 2-(6 isopropil 2-metoxi piridin-3 il)-5-(2 metoxi 1 metil-etil) 7-metil-5H-pirrolo[2 3-b]pirazina y (S)-3-etil 2-(6 isopropil 2-metoxi piridin-3-il)-5-(2-metoxi 1 metil-etil) 7-metil-5H pirrolo[2 3 b]pirazina

260



Etapa A

Se calientan 2 6-Dicloropirazina (11 7 g) (S) (+) 1 metoxi 2 propilamina (7 g) y Et_3N (15 mL) en EtOH (100 mL) a 105 C durante 2 días La mezcla se evapora y se disuelve en EtOAc y se lava con $NAHCO_3$ sat H_2O y se seca La evaporación produce 2-cloro-6 [(S) 1 metoxi 2 propil]aminopirazina LCMS m/z 202 3 y 204 3 (M+H)

Etapa B

Se disuelve 2 Cloro-6-[(S) 1 metoxi 2 propil]aminopirazina (8 3 g) en $CHCl_3$ (250 mL) Sobre adición de NBS (7 33 g) la mezcla de reacción se agita a 25 C durante 30 min Posteriormente la mezcla cruda se evapora se disuelve en EtOAc/hexano (1 4 500 mL) se lava con agua y se secan sobre sulfato de sodio

La purificación sobre gel de sílice produce 3 bromo-2-cloro-6-[(S) 1 metoxi-2 propil]aminopirazina LCMS m/z 280 2 282 2 y 284 2 (M+H)

Etapa C

Se disuelven 3 Bromo-2-cloro-6 [(S) 1 metoxi 2 propil]aminopirazina (10 7 g) y ácido 2 metoxi-6 isopropil 3 piridinoborónico (9 7 g) en DME (250 mL) Después de 10 min de desgasificación se agrega tetrakis (trifenilfosfina) paladio (0) (2 2 g) seguido por 1 min de desgasificación Sobre adición de una solución acuosa de carbonato de sodio (76 mL) la mezcla de reacción se calienta a 90 C durante 12 h Posteriormente la mezcla cruda se pone en agua (800 mL) se extrae con EtOAc/hexano (1 1 3x250 mL) y se secan sobre sulfato de sodio La purificación sobre gel de sílice produce 3-[2-cloro-6 [(S) 1 metoxi 2 propil]aminopirazin 3-il]-2 metoxi-6-isopropilpiridino LCMS m/z 351 3 y 353 3 (M+H)

Etapa D

Se disuelve 3-[2 Cloro-6-[(S) 1 metoxi 2-propil]aminopirazin 3 il]-2 metoxi-6 isopropilpiridino (4 85 g) en $CHCl_3$ (60 mL) Sobre adición de NBS (2 46 g) la mezcla de reacción se agita a 25 C durante 30 min Posteriormente la mezcla cruda se evapora se disuelve en EtOAc/hexano (1 4 250 mL) se lava con agua y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 3-[5-bromo-2-cloro-6-[(S)-1-metoxi-2 propil]aminopirazin-3-il]-2 metoxi-6-isopropilpiridino LCMS m/z 429 2 431 2 y 433 2 (M+H)

Etapa E

Se disuelve 3-[5-Bromo-2 cloro-6 [(S)-1 metoxi 2 propil]aminopirazin 3-il]-2 metoxi-6- isopropilpiridino (4 3 g) en DMSO (50 mL) Sobre adición de NaH (60% 0 8 g) la mezcla de reacción se agita a 25 C durante 30 min antes se agrega bromuro de alilo (1 7 mL) La mezcla de reacción se agita a 25 C durante 2 h Posteriormente la mezcla cruda se pone en agua (250 mL) se extrae con EtOAc/hexano (1 4 2x250 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 3-[5-bromo 2 cloro-6 [(S) N-alil 1 metoxi-2 propil]aminopirazin-3-il]-2-metoxi-6-isopropilpiridino LCMS m/z 469 3 471 3 y 473 3 (M+H)

Etapa F

Se disuelve 3-[5 Bromo 2-cloro-6 [(S) N alil 1 metoxi 2 propil]aminopirazin 3 il]-2 metoxi-6 isopropilpiridino (4 6 g) d en DMF (80 mL) Después de 10 min de desgasificación $Pd(OAc)_2$ (225 mg) se agrega seguido por 1 min de desgasificación Sobre adición de carbonato de potasio (4 1 g) y Bn_4NBr (4 0 g) la mezcla de reacción se calienta a 90 C durante 1 h Posteriormente la mezcla cruda se pone en agua (500 mL) se extrae con EtOAc/hexano (1 2 3x150 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce (S) 3 cloro-2 (6 isopropil-2-metoxi piridin-3-il) 5-(2-metoxi 1-metil-etil) 7 metil 5H pirrolo[2 3-b]pirazina LCMS m/z 389 4 y 391 4 (M+H)

Etapa G

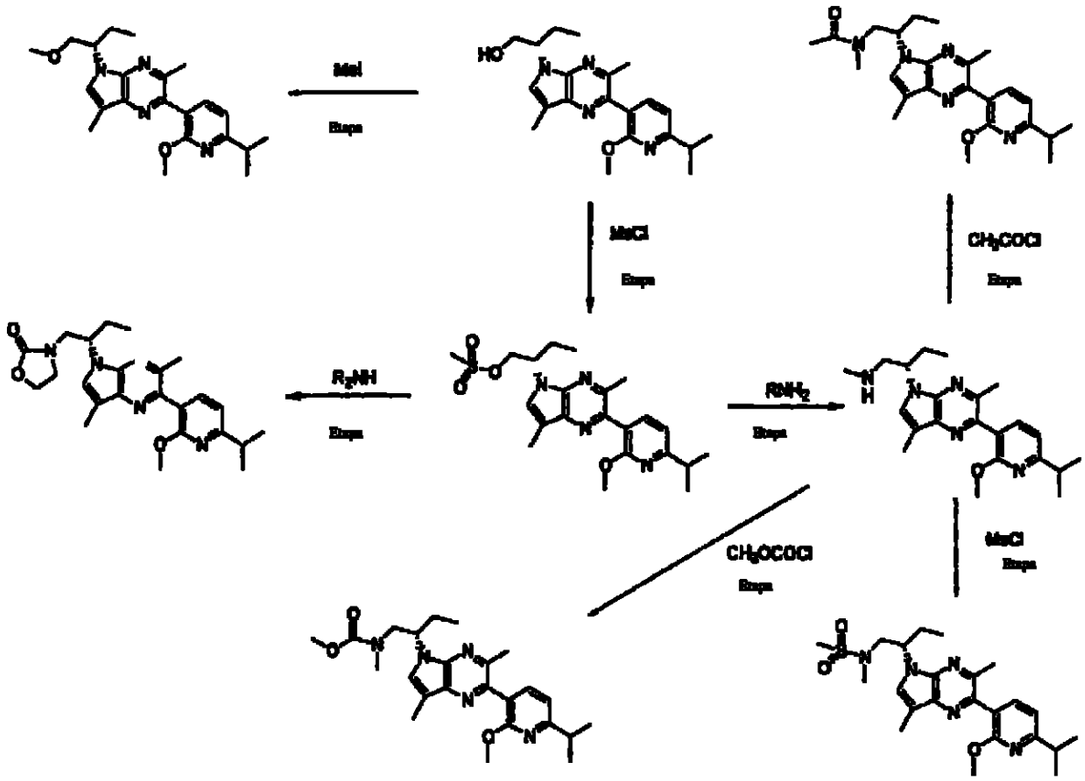
Se disuelve (S) 3-Cloro-2-(6-isopropil 2 metoxi piridin 3 il) 5 (2 metoxi 1 metil-etil) 7 metil 5H pirrolo[2 3-b]pirazina (400 mg) en tolueno (5 mL) Después de 10 min de desgasificación se agrega tetrakis (trifenilfosfina) paladio (0) (35 mg) seguido

por 1 min de desgasificación Sobre adición de trietilborano (1N en hexano 3 mL) y solución acuosa de carbonato de sodio (2 mL) la mezcla de reacción se calienta a 110 C durante 36 h Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc/hexano (1 3 3x25 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce (S) 3-etil 2 (6 isopropil-2 metoxi piridin 3 il) 5-(2-metoxi 1-metil-etil) 7 metil 5H-pirrolo[2 3 b]pirazina

LCMS m/z 383 4 (M+H)

EJEMPLO 6

Síntesis de éster de 2 [(S) 2-(6 isopropil 2-metoxi piridin-3-il)-3 7-dimetil pirrolo[2 3 b]pirazin-5-il]-butilo de ácido metanosulfónico 3-{2-[(S) 2-(6 isopropil 2-metoxi-piridin-3 il)-3 7-dimetil-pirrolo[2 3 b]pirazin-5 il] butil}-oxazolidin 2-ona {2 [(S)-2-(6 isopropil-2 metoxi-piridin-3 il)-3 7-dimetil pirrolo[2 3 b]pirazin-5-il]-butil}-metil-amina N-{2 [(S) 2-(6 isopropil 2-metoxi piridin-3-il)-3 7-dimetil-pirrolo[2 3-b]pirazin-5 il] butil}-N-metil-acetamida N {2 [(S) 2-(6 isopropil 2 metoxi-piridin-3-il)-3 7-dimetil pirrolo[2 3 b]pirazin-5 il] butil} N-metil metanosulfonamida éster de metilo de ácido {2 [(S) 2-(6 isopropil 2-metoxi piridin-3-il)-3 7-dimetil pirrolo[2 3-b]pirazin-5-il]-butil} metil-carbámico y (S)-2-(6-isopropil 2-metoxi piridin-3 il)-5-(1-metoximetil propil)-3 7-dimetil-5H-pirrolo[2 3 b]pirazina



Etapa A

Se disuelve 2 [(S) 2 (6 isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5-il] butan 1-ol (275 mg) en CH_2Cl_2 (6 mL) Se agregan MsCl (0 07 mL) y Et_3N (0 16 mL) a T.A y la mezcla se agita durante 1 h La mezcla se evapora y se disuelve en EtOAc/hexano (1 1) y se lava con $NAHCO_3$ sat H_2O y se seca La evaporación produce el metanosulfonato LCMS m/z 447 1 (M+H)

Etapa B

Se disuelve 2-Oxazolidona (26 mg) en DMF (3 mL) Se agrega NaH (12 mg 60%) a t a y la mezcla se agita durante 10 min a 85 C Sobre adición del metanosulfonato de la **Etapa A** (35 mg) la mezcla de reacción se calienta a 85 C durante 3 h Posteriormente la mezcla se vierte en H_2O y se extrae con EtOAc La

evaporación y la purificación sobre gel de sílice produce 3-{2 [(S) 2 (6-isopropil 2 metoxi pirdin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil}-oxazolidin 2-ona LCMS m/z 438 4 (M+H)

Etapa C

El anterior metanosulfonato (120 mg) de la **Etapa A** se calientan LiI (150 mg) y metilamina (7M en NMP 2 mL) a 90 C durante 4 h Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc (2xl5 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce {2-[(S) 2 (6 isopropil 2 metoxi pirdin 3 il) 3 7-dimetil-pirrolo[2 3 b]pirazin 5 il] butil}-metil-amina LCMS m/z 383 3 (M+H)

Etapa D

Se disuelve {2 [(S) 2 (6-isopropil 2 metoxi pirdin-3-il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-metil-amina (30 mg) en CH_2Cl_2 (1 mL) Cloruro de acetilo (0 017 mL) y Et_3N (0 033 mL) se agregan La mezcla resultante se agita a t a durante 30 min Posteriormente la mezcla cruda se pone en agua (2 mL) se extrae con EtOAc (2x5 mL) se lava con $NAHCO_3$ sat (2 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce N-{2 [(S) 2 (6-isopropil 2 metoxi pirdin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-N metil acetamida LCMS m/z 424 5 (M+H)

Etapa E

Se disuelve {2 [(S) 2 (6 isopropil 2-metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin-5 il] butil}-metil amina (20 mg) en CH_2Cl_2 (1 mL) Se agregan cloruro de metanosulfonilo (0 008 mL) y Et_3N (0 021 mL) La mezcla resultante se agita a t a durante 30 min Posteriormente la mezcla cruda se pone en agua (2 mL) se extrae con EtOAc (2x5 mL) se lava con $NAHCO_3$ sat (2 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce N-{2 [(S) 2 (6-isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-N-metil metanosulfonamida LCMS m/z 460 3 (M+H)

Etapa F

{2-[(S) 2 (6 isopropil 2 metoxi piridin 3 il) 3 7-dimetil-pirrolo[2 3 b]pirazin-5-il] butil}-metilamina (20 mg) se disuelve en CH_2Cl_2 (1 mL) Metil cloroformato (0 012 mL) y Et_3N (0 013 mL) se agregan La mezcla resultante se agita a t a durante 30 min Posteriormente la mezcla cruda se pone en agua (2 mL) se extrae con EtOAc (2x5 mL) se lava con $NAHCO_3$ sat (2 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce éster de metilo de ácido {2 [(S) 2 (6 isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-metil carbámico LCMS m/z 440 4 (M+H)

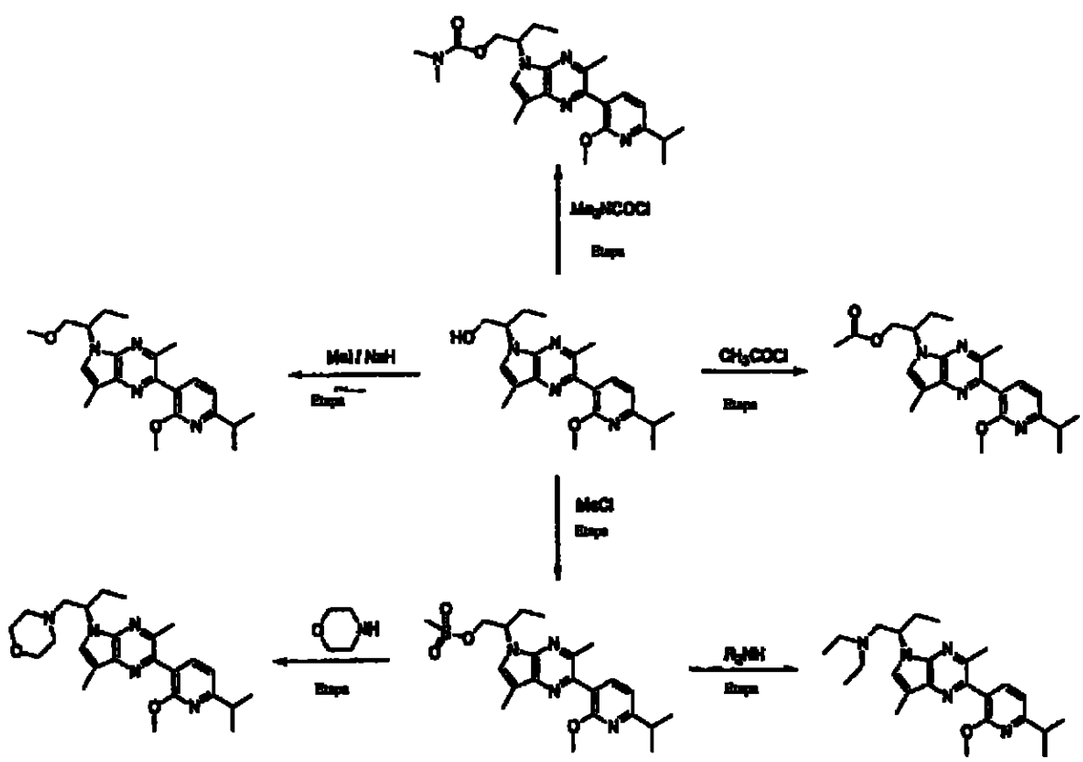
Etapa G

Se disuelve 2 [(S) 2 (6-isopropil 2 metoxi-piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butanol (40 mg) en DMF (1 mL) Se agrega NaH (60% 7 mg) seguido por CH_3I (0 02 mL) a t a y la mezcla se agita durante 1 h La mezcla se evapora y se disuelve en EtOAc/hexano (1 1) y se lava con $NAHCO_3$ sat H_2O y

se seca La evaporación produce (S) 2 (6-isopropil 2 metoxi pirıdın 3-il) 5 (1 metoxımetil propil) 3 7-dımetil 5H pırrolo[2 3 b]pırazına LCMS m/z 383 2 (M+H)

EJEMPLO 7

Síntesis de (R) 2-(6-isopropil 2-metoxi-piridin-3 il)-3 7-dimetil-5-(1 morfolin-4-ilmetil-propil)-5H-pirrolo[2 3 b]pirazina dietil-{2 [(R) 2-(6-isopropil 2 metoxi piridın-3-il)-3 7-dimetil-pirrolo[2 3-b]pirazin-5-il-butil}-amina (R) 2 (6 isopropil 2-metoxi-piridin-3 il)-5-(1-metoxımetil propil)-3 7-dimetil-5H pirrolo[2 3 b]pırazına éster de 2-[(R) 2-(6 ısopropil 2 metoxi piridin-3-il)-3 7 dimetil pirrolo[2 3-b]pirazin-5 il]-butilo acético y éster de 2 [(R) 2-(6 isopropil 2-metoxi piridin-3-il)-3 7-dimetil pırrolo[2 3-b]pırazin-5-il] butilo de ácido dimetilcarbámico



Etapa A

Se disuelve 2 [(R)-2-(6-isopropil 2 metoxi piridin-3-il)-3 7-dimetil pirrolo[2 3 b]pirazin-5 il] butan 1-ol (275 mg) en CH_2Cl_2 (6 mL) Se agregan MsCl (0 07 mL) y Et_3N (0 16 mL) a t a y la mezcla se agita durante 1 h La mezcla se evapora y se disuelve en EtOAc/hexano (1 1) y se lava con $NAHCO_3$ sat H_2O y se seca La evaporación produce el metanosulfonato LCMS m/z 447 1 (M+H)

Etapa B

El anterior metanosulfonato (95 mg) se calienta LiI (50 mg) y morfolino (0 35 mL) a 90 C durante 4 h Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc (2x15 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce (R) 2 (6 isopropil 2 metoxi piridin 3-il)-3 7-dimetil 5 (1 morfolin-4-ilmetil-propil)-5H pirrolo[2 3 b]pirazina LCMS m/z 438 5 (M+H)

Etapa C

El anterior metanosulfonato (115 mg) LiI (50 mg) y dietilamina (0 5 mL) en CH_3CN (3 mL) se calientan a 90 C durante 4 h Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc (2xl5 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce dietil-{2 [(R) 2 (6 isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil}-amina LCMS m/z 424 14 (M+H)

Etapa D

Se disuelve 2 [(R) 2 (6-isopropil 2 metoxi piridin-3 il)-3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butan 1-ol (185 mg) en DMF (2 mL) Se agrega NaH (60% 40 mg) seguido por CH_3I (0 1 mL) a t a y la mezcla resultante se agita durante 1 h La mezcla se evapora y se disuelve en EtOAc/hexano (1 1) y se lava con $NAHCO_3$ sat H_2O y se seca La evaporación produce (R) 2 (6 isopropil 2 metoxi-piridin 3 il) 5-(1 metoximetil propil)-3 7-dimetil 5H pirrolo[2 3 b]pirazina LCMS m/z 383 2 (M+H)

Etapa E

Se disuelve 2 [(R) 2 (6 isopropil-2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butan 1-ol (37 mg) en CH_2Cl_2 (1 mL) Cloruro de acetilo (0 015 mL) y Et_3N (0 028 mL) se agregan La mezcla resultante se agita a t a durante 30 min Posteriormente la mezcla cruda se pone en agua (2 mL) se extrae con EtOAc (2x5 mL) se lava con $NAHCO_3$ sat (2 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce éster de 2 [(R) 2 (6 isopropil 2 metoxi piridin 3-il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butilo LCMS m/z 411 4 (M+H)

Etapa F

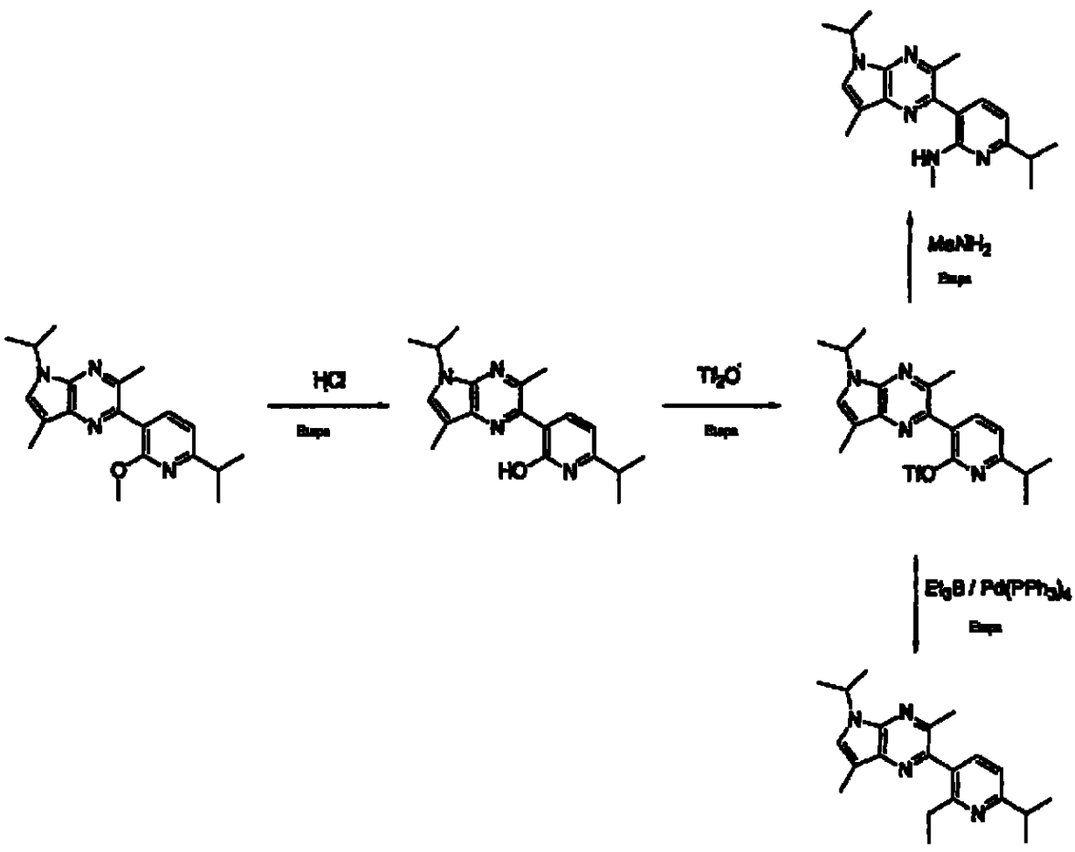
Se disuelve 2 [(R) 2 (6-isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin-5-il] butan 1-ol (70 mg) en CH_2Cl_2 (2 mL) Cloruro de Dimetilcarbamilo (0 08 mL) y piridino (0 2 mL) se agregan La mezcla resultante se agita a 75 C durante la noche Posteriormente la mezcla cruda se pone en agua (2 mL) se extrae con EtOAc (2xlO mL) se lava con $NAHCO_3$ sat (4 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce éster de 2-[(R) 2 (6

isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il]-butilo de ácido dimetilcarbámico LCMS m/z 440 4 (M+H)

EJEMPLO 8

b]pirazin 2 il) piridin 2 il]-metil-amina y 2-(2-etil-6-isopropil-piridin-3-il)

Síntesis de [6 isopropil-3-(5-isopropil-3 7-dimetil-5H-pirrolo [2 3-5 isopropil 3 7-dimetil-5H-pirrolo[2 3 b]pirazina



Etapa A

Se calienta 5 isopropil 2 (6 isopropil 2 metoxi piridin-3-il) 3 7-dimetil 5H pirrolo [2 3 b]pirazina (900 mg) en HCl (4N 6 mL) a 75 C durante 8 h La mezcla se neutraliza y se extrae con $CHCl_3$ (2x25 mL) La evaporación produce 5 isopropil 2 (6 isopropil 2 hidroxi-piridin 3-il) 3 7-dimetil-5H pirrolo[2 3 b]pirazina LCMS m/z 325 4 (M+H)

Etapa B

Se disuelve 5 isopropil 2 (6-isopropil 2 hidroxi piridin 3 il)-3 7-dimetil-5H pirrolo[2 3 b]pirazina (400 mg) en CH_2Cl_2 (8 mL) Se agregan Tf_20 (0 26 mL) y Et_3N (0 26 mL) a t a y la mezcla se agita durante 30 min La mezcla se evapora y se disuelve en EtOAc/hexano (1 1) y se lava con $NAHCO_3$ sat H_2O y se seca La evaporación produce el filtrado LCMS m/z 457 4 (M+H)

Etapa C

El anterior triflato (215 mg) y metilamina (5M en NMP 2 mL) se calientan a 90 C durante 4 h Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc/hexano (1 1 2x15 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce [6 isopropil 3 (5 isopropil 3 7-dimetil-5H pirrolo[2 3-b]pirazin 2 il) piridin 2 il] metil-amina LCMS m/z 338 3 (M+H)

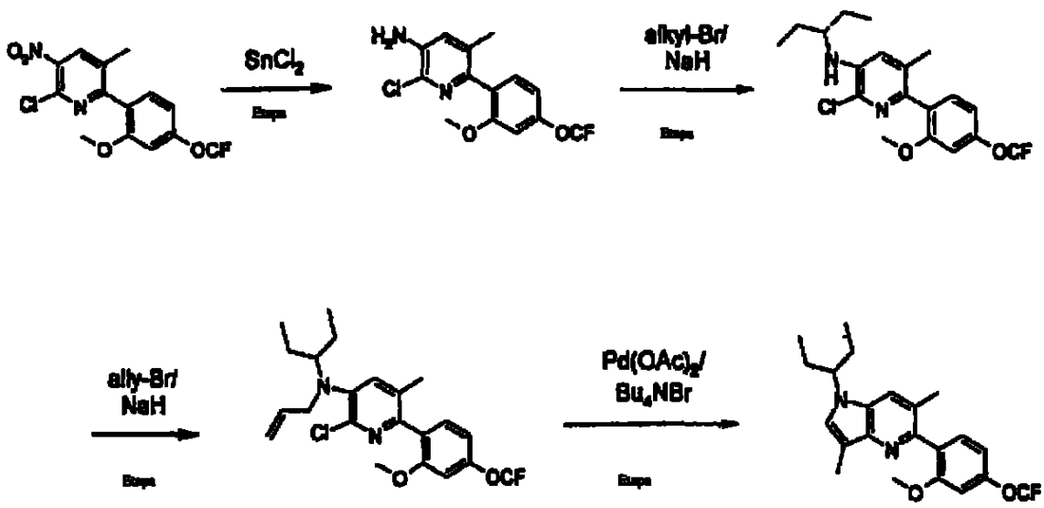
Etapa D

El anterior triflato (270 mg) se disuelve en tolueno (5 mL) Después de 10 min de desgasificación se agrega tetrakis (trifenilfosfina) paladio (0) (35 mg) seguido por 1 min de desgasificación Sobre adición de trietilborano (1N en hexano 1 8 mL)

solución acuosa de carbonato de sodio (1 2 mL) y LiCl (125 mg) la mezcla de reacción se calienta a 110 C durante 6 h Posteriormente la mezcla cruda se pone en agua (100 mL) se extrae con EtOAc/hexano (1 4 3x20 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 2 (2-etil-6-isopropil-piridin 3-il) 5-isopropil 3 7-dimetil 5H pirrolo[2 3-b]pirazina LCMS m/z 337 2 (M+H)

EJEMPLO 9

Síntesis de 1-(1-etil-propil)-5-(2-metoxi-4-trifluorometoxi fenil)-3 6-dimetil 1H pirrolo[3 2 b]piridino



Etapa A

A una solución del compuesto nitro anterior (2 63 g) en éter (30 mL) se agrega $SnCl_2x2H20$ (6 54 g) en HCl conc (20 mL) en forma de gotas a temperatura ambiente Después de que la adición se completa la mezcla de reacción se agita a temperatura ambiente durante 1 h La mezcla de reacción se basifica con NaOH

10N (se enfría con baño de hielo) a pH 9-10 Después se extrae con éter (200 mlx3) las capas de éter combinadas se secan sobre Na_2SO_4 para dar una mezcla cruda que se utiliza en la **Etapa B** sin ninguna purificación adicional ^1H RMN ($CDCl_3$ δppm) 7 26 (1H d J= 8 3 Hz) 6 93 (1H s) 6 89 (1H d J= 8 3 Hz) 6 79 (1H s) 4 03 (2H brs) 3 78 (3H s) 2 05 (3H s)

Etapa B

A una solución del producto crudo (166 mg) de la **Etapa A** en DMSO (2 mL) se agrega NaH (60% 60 mg) La mezcla de reacción se agita a TA durante 2h seguido por adición de 3-bromopentano (226 mg) Después de agitarse a TA durante 30 min la mezcla amarillenta se apaga con agua y se extrae con EtOAc La capa orgánica se lava con agua dos veces cuando la solución salina a sido finalmente secada sobre Na_2SO_4 El producto crudo se purifica sobre sílica gel ^1H RMN ($CDCl_3$ δppm) 7 26 (1H d J = 8 3 Hz) 6 87 (1H d J = 8 3 Hz) 6 77 (1H s) 6 76 (114 s) 4 13 (1H d J= 8 6 Hz) 3 74 (3H s) 3 24~3 29 (1H m) 2 07 (3H s) 1 59 1 69 (2H m) 1 49~1 59 (2H m) 0 97 (6H t J= 7 3 Hz)

Etapa C

A una solución del producto de alquilación de la Etapa B (403 mg) en NMP (2 mL) y bromuro de tetrabutilamonio (cat) se agrega NaH (60% 120 mg) La mezcla de reacción se agita a TA durante 2 h seguido por adición de bromuro de alilo (2 eq) Después se agita a 60 C durante 3 h la mezcla se apaga con agua se extrae con EtOAc y se seca sobre Na_2SO_4 El producto crudo se purifica on sílica gel ^1H RMN ($CDCl_3$ δppm) 7 29 (1H d J= 8 2 Hz) 7 17 (1H s) 6 86 (1H d J= 8 2 Hz) 6 76 (1H brs) 5 66~5 75 (1H m) 5 18 (1H d J= 18Hz) 5 05 (1H d J= 10Hz)

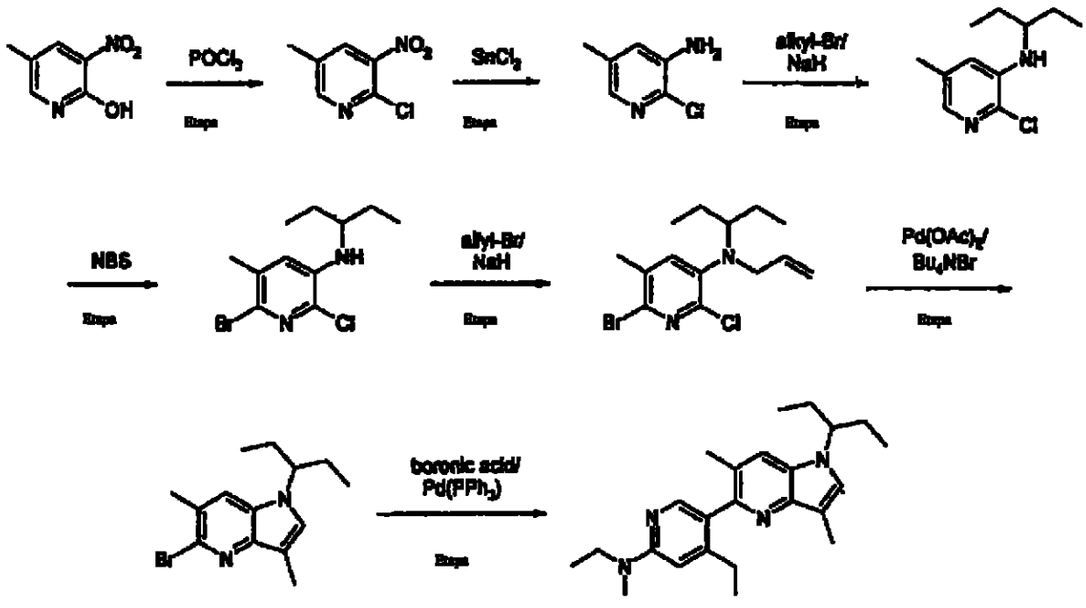
3 77~3 81 (5H CH_2 CH_3) 3 32 (1H m) 2 07 (3H s) 1 54 1 63 (4H m) 0 95 (6H t J= 7 5 Hz)

Etapa D

Una mezcla de alilamina de la Etapa C (100 mg) $Pd(OAc)_2$ (5 1 mg) bromuro de tetrabutilamonio (72 9 mg) y K_2CO_3 (93 mg) en DMF (3 mL) se desgasifica y luego se calienta a 80 C durante la noche La mezcla posteriormente se apaga con agua se extrae con EtOAc y se seca sobre Na_2SO_4 La purificación sobre gel de sílice produjo el compuesto del título ^1H RMN ($CDCl_3$ δppm) 7 43 (1H s) 7 35 (1H d J=8 3Hz) 7 08 (1H d J = 1 0 Hz) 6 91~6 94 (1H dm) 6 80 (1H brs) 3 99 (1H m) 3 77 (3H s) 2 40 (3H s) 2 21 (3H s) 1 85-1 91 (4H m) 0 80 (6H brs)

EJEMPLO 10

Síntesis de etil-{4-etil-5 [1-(1-etil-propil)-3 6-dimetil 1H-pirrolo[3 2 b]piridin-5-il] piridin 2 il}-metil-amina



Etapa A

El nitropirdino mostrado (25 g) en $POCl_3$ (100 mL) se refluye durante 8 h Después que la reacción se completa la mezcla de reacción se concentra a presión reducida hasta sequedad Se agrega hielo (100 g) a el residuo cuando este se neutraliza con NaOH 2N La extracción con EtOAc (200 mLx2) y secado sobre $MgSO_4$ produjo un producto crudo que es utilizado en la **Etapa B** sin ninguna purificación adicional

Etapa B

A una solución del compuesto de cloro de la **Etapa A** (20 g) en etanol (300 mL) se agrega $SnCl_2x2H20$ (132 g) en forma de porciones Después que la adición se completa la mezcla se agita adicionalmente durante 2 h a 50 C antes el solvente se remueve bajo presión reducida DCM (400 mL) se agrega y la suspensión se neutraliza con NaOH 10N y luego se filtra a través de celita El filtrado se lava con agua solución salina y finalmente se seca sobre $MgSO_4$ para producir la amina La mezcla cruda se utiliza en la **Etapa C** sin ninguna purificación adicional

Etapa C

A una solución de la amina (13 5 g) de la **Etapa B** en NMP (80 mL) se agrega bromuro de tetrabutilamonio (0 3 g) y NaH (60% 7 6 g) a 0 C Después de agitarse a TA durante 3h se agrega 3 bromopentano (1 5 eq) La mezcla de reacción se agita luego adicionalmente durante 2 h antes se apaga con agua y se extrae con EtOAc La capa orgánica se lava con agua solución salina y se seca

sobre $MgSO_4$ La evaporación bajo presión reducida produjo un producto crudo que es utilizado en **Etapa D** sin ninguna purificación adicional ^1H RMN ($CDCl_3$ δppm) 7 48 (1H s) 6 67 (1H s) 4 07 (1H d J= 8 2Hz) 3 2~3 24 (1H m) 2 23 (3H s) 1 48-1 68 (4H m) 0 93 (6H t J= 7 3 Hz)

Etapa D

El material crudo de la Etapa C (3 0 g) se disuelve en $CHCl_3$ (20 mL) y se agrega NBS (2 63 g) a temperatura ambiente Después de agitarse a TA durante 30 min la mezcla de reacción se lava con agua solución salina y se seca sobre Na_2SO_4 antes se purifica sobre gel de sílice para producir el bromuro ^1H RMN ($CDCl_3$ δppm) 6 74 (1H s) 4 04 (1H d J= 7 8Hz) 3 17~3 22 (1H m) 2 29 (3H s) 1 47 1 56 (2H m) 1 56 1 66 (2H m) 0 93 (6H t J= 7 4 Hz)

Etapa E

A una solución del bromuro de la **Etapa D** (3 66 g) en NMP se agrega bromuro de tetrabutilamonio (O I g) y NaH (60% 1 O g) a ta Después de agitarse a TA durante 3 h se agrega bromuro de alilo (3 0 g) y la mezcla de reacción se agita adicionalmente durante 4 h La mezcla de reacción se apaga con agua y se extrae con EtOAc La capa orgánica se lava con agua solución salina y se seca sobre $MgSO_4$ para producir un producto crudo que es utilizado en etapa F sin ninguna purificación adicional ^1H RMN ($CDCl_3$ δppm) 7 11 (1H s) 5 56 5 66 (1H m) 5 13 (1H d J = 17 4Hz) 5 13 (1H d J= 10Hz) 3 70 3 72 (2H m) 3 22~3 26 (1H m) 2 29 (3H s) 1 52 1 60 (4H m) 0 91 (6H t J= 7 4Hz)

Etapa F

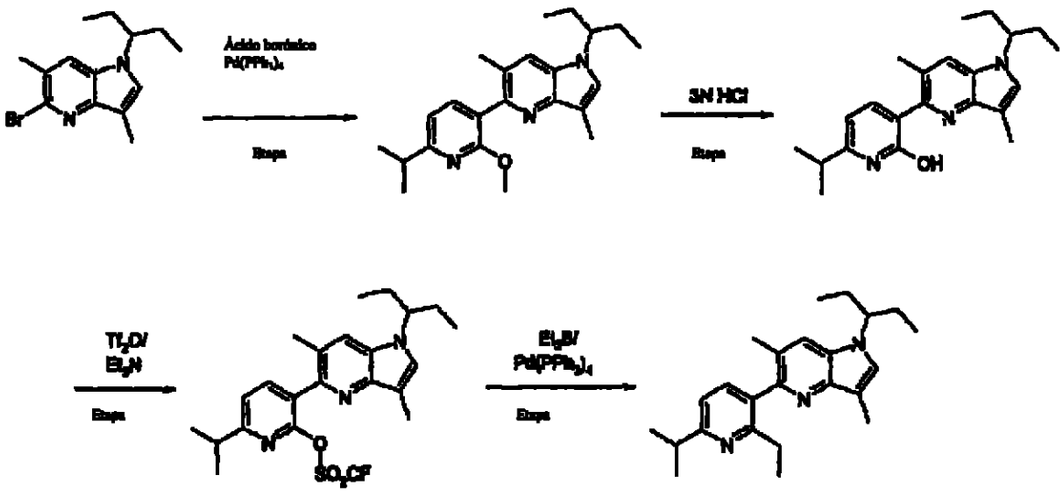
El material crudo de la Etapa E (4 1 g) $Pd(OAc)_2$ (275 mg) bromuro de tetrabutilamonio (4 5 g) y K_2CO_3 (5 1 g) se disuelven en DMF (20 mL) Después de desgasificar la mezcla se calienta a 80 C durante la noche La solución negra se diluye con EtOAc antes se lava con H_2O solución salina y se seca sobre $MgSO_4$ La purificación sobre gel de sílice produjo el compuesto bicíclico ^1H RMN ($CDCl_3$ δppm) 7 43 (1H s) 7 05 (1H s) 3 89-3 92 (1H m) 2 48 (3H s) 2 36 (3H s) 1 76-1 88 (4H m) 0 72 (6H t J= 7 3 Hz)

Etapa G

El material bicíclico de la etapa F (118 mg) $Pd(PPh_3)_4$ (70 mg) y el ácido 4-etil-2 etilmetilamino-3 pirídino borónico previamente descrito (104 mg) se disuelven en tolueno (10 mL) Sobre adición de Na_2CO_3 2N (4 mL) la mezcla se desgasifica y luego se calienta durante la noche a 80 C Posteriormente la mezcla se diluye con EtOAc y se lava con H_2O solución salina y finalmente se seca sobre $MgSO_4$ La purificación sobre gel de sílice produjo el compuesto del título ^1H RMN ($CDCl_3$ δppm) 8 00 (1H s) 7 43 (1H s) 7 07 (1H brs) 6 45 (1H s) 3 96-4 01 (1H m) 3 62 (2H q J= 7 0 Hz) 2 48 (3H s) 3 06 (3H s) 2 42 (2H q J= 7 5 Hz) 2 39 (3H s) 2 23 (3H s) 1 81 1 90 (4H m) 1 18 (3H t J= 7 2 Hz) 1 03 (3H t J= 7 5 Hz) 0 81 (6H t J= 7 3 Hz)

EJEMPLO 11

Síntesis de 5-(2-etil-6 isopropil piridin-3 il) 1-(1-etil propil)-3 6-dimetil 1H pirrolo[3 2 b]piridino



Etapa A

El previamente descrito bromuro bicíclico (590 mg) el ácido 6 isopropil 2 metoxi 3 pindino borónico también previamente descrito (507 mg) y $Pd(PPh_3)_4$ (115 mg) se disuelven en tolueno (30 mL) Sobre adición de Na_2CO_3 2N (6 mL) la mezcla se desgasifica y luego se calienta durante la noche a 85 C Posteriormente la mezcla se diluye con EtOAc y se lava con NaOH 2N H_2O solución salina y finalmente se seca sobre $MgSO_4$ La purificación sobre gel de sílice produjo el producto acoplado ^1H RMN ($CDCl_3$ δppm) 7 55 (1H d J= 7 3 Hz) 7 42 (1H s) 7 06 (1H d J= 1 1 Hz) 6 84 (1H d J= 7 5 Hz) 3 96-4 00 (1H m) 3 91 (3H s) 2 98 3 01 (1H m) 2 39 (3H d J= 1 1 Hz) 2 25 (3H s) 1 82 1 90 (4H m) 1 31 (6H d J= 7 0Hz) 0 80 (6H t J= 7 5 Hz)

Etapa B

El producto Suzuki de la Etapa A (718 mg) se disuelve en HCl 3N (50 mL) y se calienta a 70 C durante la noche La mezcla de reacción se enfría a temperatura ambiente se neutraliza con NaOH 2N y se extrae con $CHCl_3$ (100 mlx2) Se seca

sobre $MgSO_4$ produjo la pirrolona que es utilizada en la **Etapa C** sin ninguna purificación adicional

Etapa C

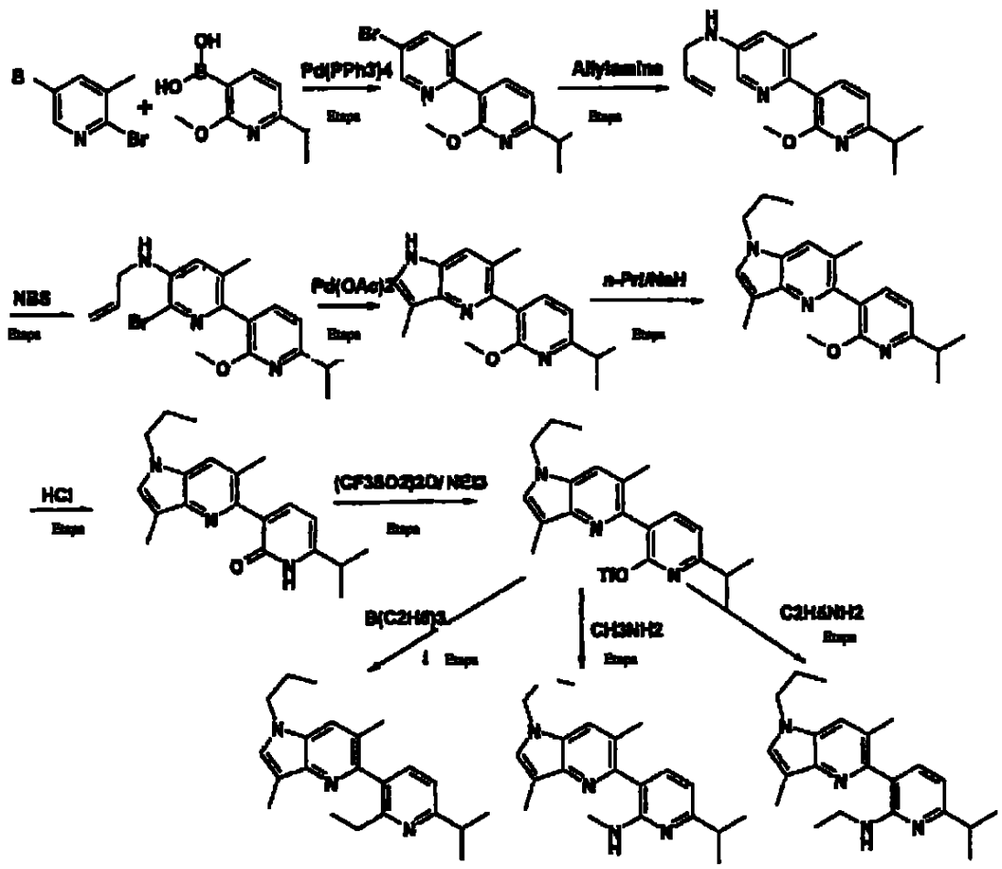
La pirrolona (700 mg) de la Etapa B se disuelve en CH_2Cl_2 Se agrega trietilamina (3 eq) seguido de adición en forma de gotas de Tf_2O (1 5 equivalentes) a 0 C Después de agitarse a TA durante 2 h la mezcla de reacción se lava con H_2O solución salina y se seca sobre $MgSO_4$ El filtrado se utiliza en la **Etapa D** sin ninguna purificación adicional

Etapa D

El material crudo de la Etapa C (48 mg) $Pd(PPh_3)_4$ (11 5 mg) y trietilborano (0 5 ml en in hexano) se disuelven en tolueno (2 mL) Después de adición de Na_2CO_3 2N (0 5 mL) la mezcla se desgasifica y luego se calienta a 85 C durante la noche La solución se diluye con EtOAc y se lava con NaOH 2N H_2O solución salina y finalmente se seca sobre $MgSO_4$ La purificación sobre gel de sílice produjo el compuesto del título ^1H RMN ($CDCl_3$ δppm) 7 46 (1H d J= 7 9 Hz) 7 44 (1H s) 7 09 (1H d J= 0 8 Hz) 7 06 (1H d J= 7 7 Hz) 3 97-4 01 (1H m) 3 10 3 13 (1H m) 2 60 (2H q J= 7 3Hz) 2 39 (3H d J= 0 8 Hz) 2 16 (3H s) 1 81 1 90 (4H m) 1 32 (6H d J= 7 0Hz) 1 15 (3H t J= 7 3Hz) 0 80 (6H t J= 7 6 Hz)

EJEMPLO 12

Síntesis de 5-(2-etil-6 isopropil-piridin-3 il)-3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridino [3-(3 6-dimetil 1-propil 1H pirrolo[3 2 b]piridin-5-il)-6-isopropil pirídin 2-il] metil-amina y [3 (3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridin-5-il) 6 isopropil piridin 2-il]-etil-amina



Etapa A

Una mezcla de 2 5-dibromo-3 metilpirídino (5 02g 0 02mol)) ácido 2 metoxi-6 isopropil 3 pirídilborónico (4 10 g 0 021 mol) $Pd(PPh_3)_4$ (924 mg) solución acuosa de Na_2CO_3 (1 0M 40ml) y tolueno (50 mL) se calienta a 100 C bajo atmósfera de N_2 durante la noche La mezcla de reacción se enfría a temperatura ambiente y se separa La capa acuosa se extrajo con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La

purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro LCMS m/z 323 3 (M+H)

Etapa B

Una mezcla de bromuro (9 63g 0 03mol) alilamina (6 75 mL) BINAP (1 5 g) $Pd_2(dba)_3$ (1 0 g) NaO *t* Bu (5 77 g) en tolueno (150 mL) se calienta a 100 C bajo atmósfera de N_2 durante la noche La mezcla de reacción se enfría a temperatura ambiente y se apaga con agua La mezcla resultante se separa y se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro LCMS m/z 298 3 (M+H)

Etapa C

El material de partida (6 67 g) se pone en $CHCl_3$ anhidro (100 mL) Se agrega 1 0 equivalente de NBS en una porción a 0 C la reacción se completa en 0 5 horas La mezcla de reacción se lava con solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro LCMS m/z 376 4 (M+H)

Etapa D

Una mezcla de bromuro (6 6 g) bromuro de tetrabutilamonio (7 07 g) K_2C0_3 (7 28 g) $Pd(OAc)_2$ (150 mg) en DMF (70 mL) se calienta a 80 bajo atmósfera de N_2 durante 0 5 hora La mezcla de reacción se enfría a temperatura ambiente y se diluye con agua La mezcla resultante se extrajo con acetato de etilo Las capas

orgánicas combinadas se lavan con solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como sólido blanco LCMS m/z 296 4 (M+H)

Etapa E

Se agrega NaH (100 mg 60% en aceite mineral) a una solución de material de partida (58 mg) en DMF anhidro (5 mL) y se agita durante 10 minutos 1 yodopropano (0 5 mL) se agrega y agita durante 05 horas La mezcla de reacción cuidadosamente se apaga con 1 ml de metanol y se diluye con agua La mezcla resultante se extrajo con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro LCMS m/z 338 4 (M+H)

Etapa F

El material de partida (360 mg) se coloca en HCl 4N (20 mL) y se calienta a 75 C durante la noche La mezcla de reacción se enfría a 0 C y el valor de pH se ajusta a ~12 por agregar solución acuosa de NaOH 10N La mezcla resultante se extrajo con cloroformo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La concentración da el producto crudo como un sólido blanco Este se utiliza durante la siguiente etapa de reacción sin purificación adicional LCMS m/z 324 4 (M+H)

Etapa G

Se pone la pirídona (330 mg) en cloruro de metileno anhidro (20 mL) y se enfría a 0 C anhídrido tríflico (1 5 equiv) se agrega seguido por la adición de trietilamina (2 equiv) La reacción se completa en 0 5 hora La mezcla de reacción se lava con $NaHCO_3$ saturado y se seca con Na_2SO_4 El producto crudo se utiliza durante la siguiente etapa de reacción sin purificación adicional LCMS m/z 456 4 (M+H)

Etapa H

Una mezcla de triflato (80 mg) LiCl (84 mg) $Pd(PPh_3)_4$ (23 mg) Na_2CO_3 (1 0M en agua 1 mL) $B(C_2H_5)_3$ (1 0M en hexano 1 5 mL) en tolueno (2ml) se calienta a 100 C en tubo sellado durante 2 horas La mezcla resultante se enfría a temperatura ambiente y se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da 5-(2-etil-6-isopropil-pirídin 3 il) 3 6-dimetil-1 propil 1H pirrolo[3 2 b]piridino como aceite claro LCMS m/z 336 4 (M+H)

Etapa I

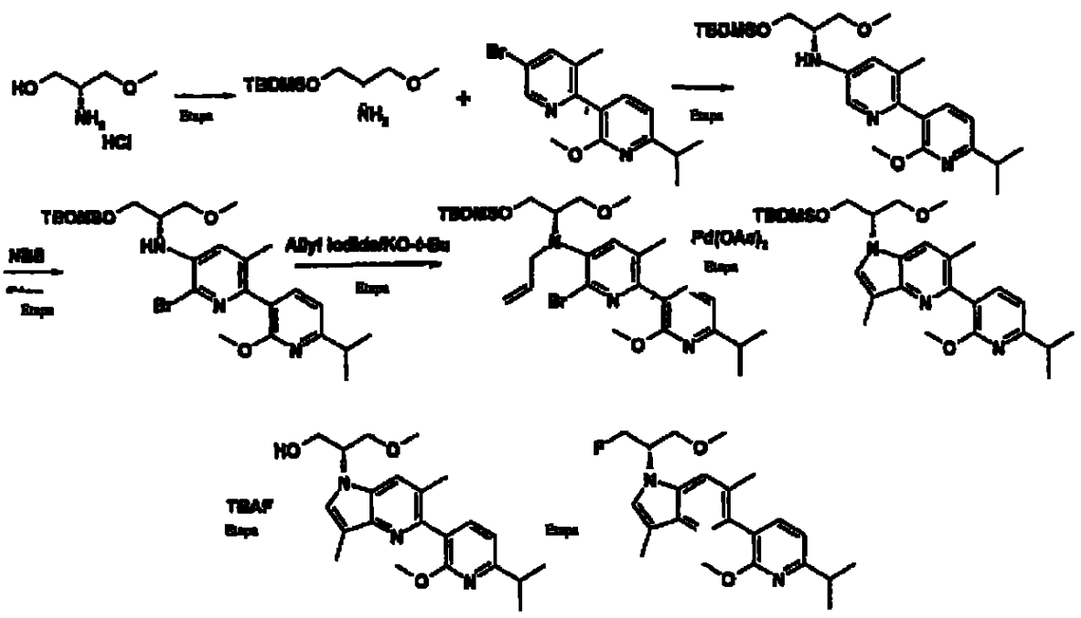
Se pone triflato (230 mg) en N metilpirrolidinona anhidro (2 mL) se agrega CH_3NH_2 como una solución de NMP (5 5M 2 mL) La mezcla resultante se calienta a 85 C en un tubo sellado durante la noche La mezcla de reacción se enfría a temperatura ambiente y se diluye con agua La mezcla resultante se extrajo con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da [3-(3 6-dimetil 1 propil 1H pirrolo[3 2 b]pirídin 5-il)-6-isopropil pirídin 2 il] metil amina como aceite claro LCMS m/z 337 4 (M+H)

Etapa J

Se pone triflato (420 mg) en N metilpirrolidinona anidro (3 mL) se agrega $C_2H_5NH_2$ como una solución de THF (2 0 M 2 mL) La mezcla resultante se calienta a 85 C en un tubo sellado durante la noche La mezcla de reacción se enfría a temperatura ambiente y se diluye con agua La mezcla resultante se extrajo con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da [3-(3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridin 5 il)-6 isopropil piridin 2 il] etil-amina como aceite claro LCMS m/z 351 5 (M+H)

EJEMPLO 13

Síntesis de (R) 2 [5-(6 isopropil 2-metoxi-piridin-3-il)-3 6-dimetil pirrolo[3 2 b]piridin 1 il]-3-metoxi propan 1-ol y 1-((S) 2 fluoro 1-metoximetil-etil)-5-(6 isopropil 2-metoxi-piridin-3 il)-3 6-dimetil 1H pirrolo[3 2 b]piridino



Etapa A

Clorhidrato de (R) 2-Amino-3 metoxi propan 1 ol (CAS# 148278 96 0) (6 74 g) e imidazol(13 2 g) se colocan en cloruro de metileno anhidro (300 mL) TBDMSCl (21 9 g) se agrega en una porción La reacción se lleva durante la noche La mezcla de reacción se lava con agua (200 mlX3) y se seca con Na_2SO_4 La concentración remueve todos los volátiles El producto crudo se utiliza para la siguiente etapa de reacción sin purificación adicional

Etapa B

Una mezcla de bromuro (6 42g 0 02mol) amina (1 5equiv) BINAP (1 0 g) Pd2 (dba) 3 (0 6 g) NaO *t* Bu (4 0 g) en tolueno (80 ml) se calienta a 85 C bajo atmósfera de N_2 durante la noche La mezcla de reacción se enfría a temperatura ambiente y se apaga con agua La mezcla resultante se separa y se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro Rf 0 3 (Hexano/acetato de etilo 3/1)

Etapa C

El material de partida (7 33 g) se pone en $CHCl_3$ anidrido (100 mL) Se agrega 1 0 equivalente de NBS en una porción a 0 C La reacción se completa en 0 5 horas La mezcla de reacción se lava con solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro Rf 0 3 (Hexano/acetato de etilo 15/1)

Etapa D

El material de partida (5 94 g) se pone en THF anhidro (100 mL) Se agrega yoduro de alilo (3 6 mL) seguido por la adición de solución de KO *t* Bu/THF (1 0M 44 mL) a temperatura ambiente La reacción se agita a temperatura ambiente durante 3 horas La mezcla de reacción se apaga con agua La mezcla resultante se separa y se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se seca con Na_2S0_4 El producto crudo es utilizado durante la siguiente etapa de reacción sin purificación adicional Rf 0 3 (Hexano/acetato de etilo 19/1)

Etapa E

El producto crudo (6 4 g) de la reacción previa se pone en DMF (60 mL) seguido por la adición de bromuro de tetrabutilamonio (4 45 g) K_2CO_3 (4 58 g) $Pd(OAc)_2$ (125 mg) La mezcla resultante se calienta a 85 C bajo atmósfera de N_2 durante una hora La mezcla de reacción se enfría a temperatura ambiente y se diluye con agua La mezcla resultante se extrajo con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro 0 3 (Hexano/acetato de etilo 5/1)

Etapa F

El material de partida (5 43 g) se pone en THF (60 mL) seguido por la adición de fluoruro de tetrabutilamonio (2 equiv) a temperatura ambiente La reacción se completa después de 2 horas La mezcla de reacción se lava con agua solución

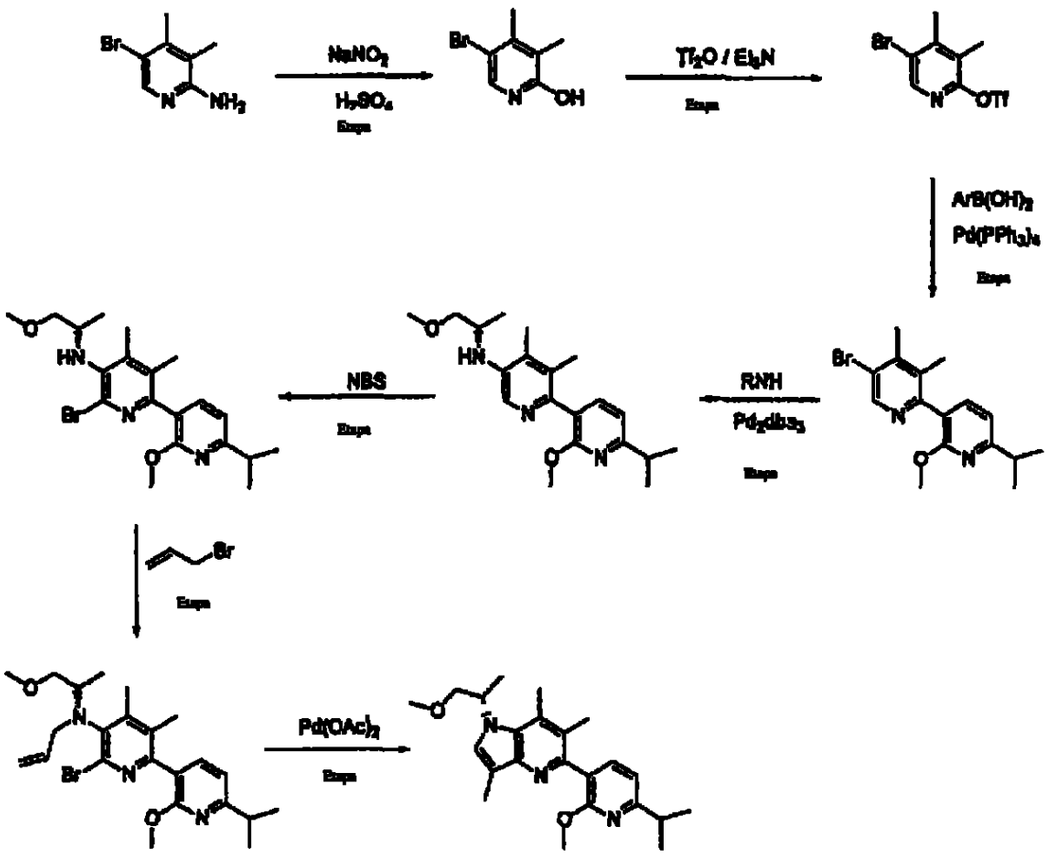
salina y se seca con Na_2SO_4 La concentración da (R) 2 [5 (6 isopropil 2 metoxi pindin 3 il) 3 6-dimetil-pirrolo[3 2 b]pindin 1 il] 3 metoxi propan 1-ol como como un sólido blanco LCMS m/z 384 4 (M+H)

Etapa G

El material de partida (1 15g 3 mmol) se pone en cloruro de metileno anhidro (50 mL) seguido por la adición de trifluoruro de [Bis (2 metoxietil) amino] sulfuro (2 equiv) a temperatura ambiente La reacción se agita a temperatura ambiente durante la noche La mezcla de reacción cuidadosamente se apaga con agua helada La mezcla resultante se separa y se extrae con cloruro de metileno y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da 1 ((S) 2 fluoro-1 metoximetil-etil)-5-(6 isopropil-2 metoxi pindin 3 i)-3 6-dimetil 1H pirrolo[3 2-b]pindino como aceite claro 0 3 (Hexano/acetato de etilo 5/1)

EJEMPLO 14

Síntesis de 5-(6 Isopropil 2 metoxi-piridin-3-il) 1 ((S) 2 metoxi 1-metil-etil) 3 6 7 trimetil 1H pirrolo[3 2-b]pindino



Etapa A

Se enfría 2 Amino-5-bromo-3 4-dimetilpiridino (201 mg) en H_2S0_4 (2 5N 2 4 mL) a 0 C y posteriormente se trata en forma de gotas con nitrito de sodio (104 mg) en H_2O (1 mL) El sólido se recolecta y se lava con H_2O y se seca para producir 2 hidroxi 5 bromo 3 4-dimetilpiridino LCMS m/z 202 2 y 204 2 (M+H)

Etapa B

Se disuelve 2 Hidroxi 5-bromo 3 4-dimetilpiridino (165 mg) en $CHCl_3$ (3 mL) Se agregan anhidrido trífilico (0 17 mL) y Et_3N (0 17 mL) a t a y la mezcla se agita durante 30 min La mezcla se evapora y se disuelve en EtOAc/hexano (2 8) y se

lava con $NAHCO_3$ sat H_2O y se seca La evaporación produce el filtrado LCMS m/z 334 0 y 336 0 (M+H)

Etapa C

El anterior triflato (272 mg) y ácido 2-metoxi-6 isopropil 3 piridinoborónico se disuelve en DME (3 5 mL) Después de 10 min de desgasificación se agrega tetrakis (trifenilfosfina) paladio (0) (12 mg) seguido por 1 min de desgasificación Sobre adición de una solución acuosa de carbonato de sodio (1 63 mL) y LiCl (140 mg) la mezcla de reacción se calienta a 90 C durante 16 h Posteriormente la mezcla cruda se pone en agua (100 mL) se extrae con EtOAc/hexano (20 80 3x20 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 3 (5-bromo-3 4-dimetil piridin 2 il) 2 metoxi-6 isopropilpiridino LCMS m/z 335 1 y 337 1 (M+H)

Etapa D

Se disuelven 3-(5-bromo-3 4-dimetil piridin 2 il) 2 metoxi-6 isopropilpiridino (85 mg) (S) 2 metoxi 1 metil-etilamina (34 mg) Pd_2dba_3 (12 mg) BINAP (16 mg) y t BuONa (37 mg) en tolueno (3 5 mL) La mezcla de reacción se calienta a 90 C durante 6 h Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc/hexano (1 1 2xl O mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 3-[5 [(S) 2 metoxi-1 metil-etilamino]-3 4 dimetil piridin 2 il]-2 metoxi-6 isopropilpiridino LCMS m/z 344 4 (M+H)

Etapa E

Se disuelve 3-{5-[(S) 2 metoxi 1 metil-etilamino]-3 4-dimetil piridin 2 il}-2 metoxi-6-isopropilpiridino (42 mg) en $CHCl_3$ (l mL) Sobre adición de NBS (24 mg) la mezcla de reacción se agita a 25 C durante 30 min Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc/hexano (1 4 2x5 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 3-{6-bromo-5-[(S) 2 metoxi 1 metil-etilamino] 3 4-dimetil piridin 2 il}-2 metoxi-6 isopropilpiridino LCMS m/z 422 3 y 424 3 (M+H)

Etapa F

Se disuelve 3-{6 bromo 5-[(S)-2 metoxi-1 metil-etilamino] 3 4-dimetil-pirdin 2 il}-2 metoxi-6-isopropilpiridino (2 0 g) en NMP (15 mL) Sobre adición de NaH (60% 380 mg) la mezcla de reacción se agita a 25 C durante 30 min antes se agrega bromuro de alilo (0 82 mL) La mezcla de reacción se calienta a 50 C durante la noche Posteriormente la mezcla cruda se pone en agua (10 mL) se extrae con EtOAc/hexano (1 4 2x50 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 3-{6-bromo-5-[(S) N-alil 2 metoxi-1 metil-etilamino]-3 4 dimetil-pirdin 2 il}-2 metoxi-6 isopropilpirdino LCMS m/z 462 4 y 464 4 (M+H)

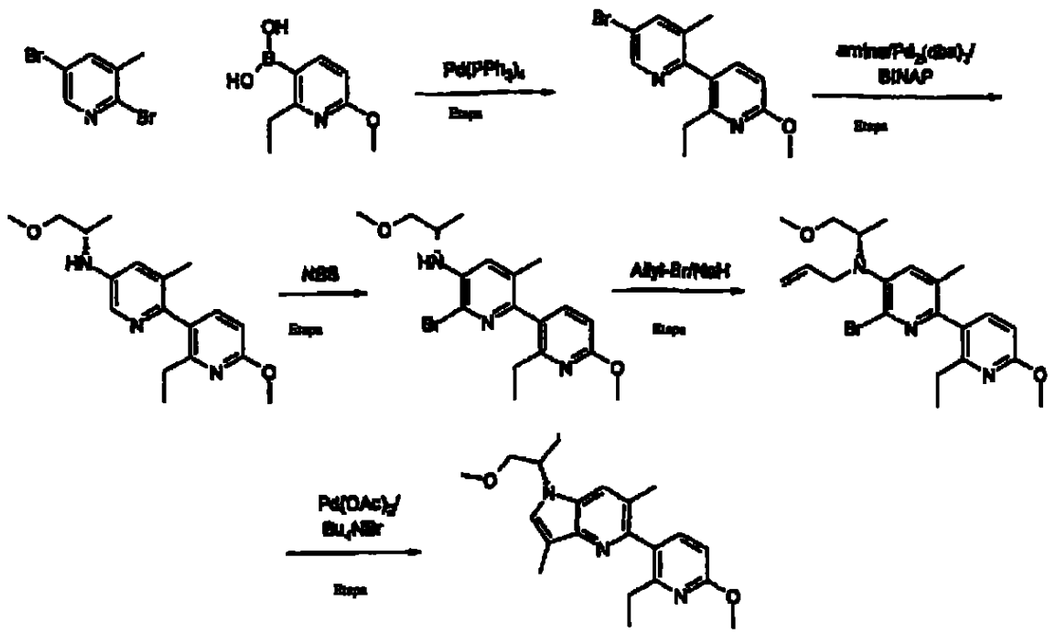
Etapa G

Se disuelve 3-{6 bromo-5 [(S) N-alil 2 metoxi 1 metil-etilamino]-3 4-dimetil pirdin 2 il}-2 metoxi-6 isopropilpirdino (0 75 g) en DMF (6 mL) Después de 10 min de desgasificación se agrega $Pd(OAc)_2$ (36 mg) seguido por 1 min de desgasificación Sobre adición de carbonato de potasio (670 mg) y Bn_4NBr (650 mg) la mezcla de reacción se calienta a 90 C durante 2 h Posteriormente la mezcla cruda se pone en agua (100 mL) se extrae con EtOAc/hexano (1 2 3x50

mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce 5 (6 isopropil 2-metoxi-pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-3 6 7 trimetil 1H pirrolo[3 2 b]pirdino LCMS m/z 382 3 (M+H)

EJEMPLO 15

Síntesis de 5-(2-etil-6-metoxi piridin-3-il) 1-((S) 2-metoxi 1 metil-etil)-3 6 dimetil 1H pirrolo[3 2-b]piridino



Etapa A

Se disuelven 2 5-dibromo-3-metilpirdino (18 90 g) y el ácido 2-etil-6 metoxi-3-pirdino borónico previamente descrito (13 70 g) en DME (200 mL) Después de desgasificar se agrega tetrakis (trifenilfosfina) paladio (0) (3 60 g) Una segunda desgasificación es seguida por adición de una solución de carbonato de sodio 5N (30 mL) con lo cual la reacción se calienta a 80 C durante 16 h La mezcla

amarillenta se coloca entonces en agua (500 mL) se extrae con DCM (2x300 mL) y se seca sobre sulfato de sodio La purificación sobre gel de sílice produce el producto acoplado LCMS m/z 306 94 (M+H)

Etapa B

El compuesto purificado (6 40 g) de la Etapa A y (S) 1 metoxi 2-aminopropano (2 04 g) se disuelven en tolueno (80 mL) y se desgasifican brevemente Posteriormente se agregan $Pd_2(dba)_3$ (1 03 g) *rac*-2 2 bis (difenilfosfino) 1 1 binaftil (0 76 g) y *terc*-butóxido de sodio (2 81 g) se agregan antes la mezcla se calienta a 70 C durante 16 h La solución negra se coloca entonces en agua (400 mL) y bicarbonato de sodio saturado (100 mL) se extrae con DCM (3x300 mL) y se seca sobre sulfato de magnesio El material crudo fue lavado a chorro a través de un tapón de gel de sílice produce el 5 aminopiridino como un semi-crudo que se utiliza en la Etapa C LCMS m/z 316 35 (M+H)

Etapa C

El compuesto aminode la Etapa B se disuelve en cloroformo (200 mL) y se agrega NBS (0 9 1 0 eq) en porciones hasta que el control TLC verifica la conversión completa del material de partida Posteriormente la mezcla amarillenta se pone en agua (200 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el bromuro LCMS m/z 394 21 (M+H)

Etapa D

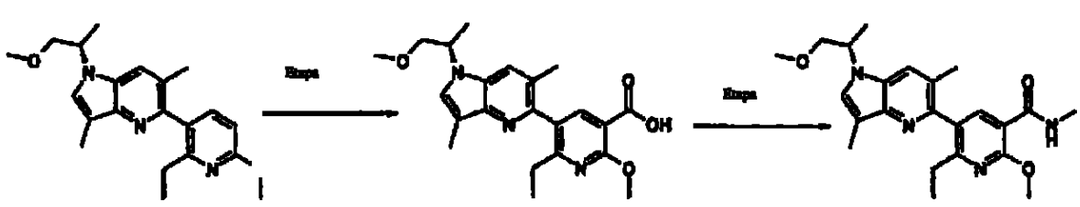
El bromuro purificado (7 59 g) de la Etapa C y bromuro de alilo (2 04 mL) se disuelven en DMF (100 mL) Se agrega hidruro de sodio (1 16 g) en 3 porciones y la reacción se agita durante 90 min a ta Después el control TLC confirma que algunos de los materiales de partida todavía quedan se agregan 0 25 equivalentes de ambos reactivos para dar terminación a la reacción La mezcla se coloca entonces en agua (500 mL) y se extrae con éter de etilo (2x300 mL) Las capas orgánicas combinadas se lavan con agua (100 mL) se secan sobre sulfato de magnesio y se purifican sobre gel de sílice para producir la amina alilatada LCMS m/z 434 23 (M+H)

Etapa E

El compuesto alilo (7 89 g) de la Etapa D se disuelven bromuro de tetrabutilamonio (5 85 g) acetato de paladio (0 41 g) y carbonato de potasio (7 53 g) en DMF (150 mL) Después de calentar a 80 C durante 30 min la mezcla se trabaja de acuerdo con la Etapa D La purificación final sobre gel de sílice produce el compuesto del título LCMS m/z 354 39 (M+H)

EJEMPLO 16

Síntesis de 6-etil 2-metoxi-5-[1-((2-metoxi 1-metil-etil)-3 6-dimetil 1H pirrolo[3 2-b]piridin-5 il] N-metil-nicotinamida



Etapa A

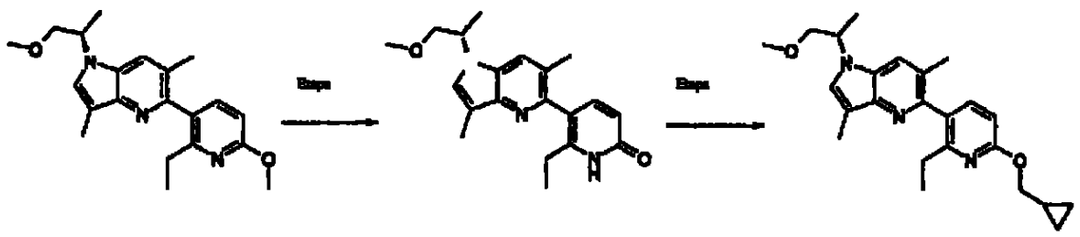
Se disuelve 5 (2 Etil-6-metoxi-piridin 3 il)-1-((S) 2-metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridino (135 mg) en THF (10 mL) y luego se enfría a –40 C Sobre adición de *t* BuLi (0 45 ml 1 7N en pentano) la temperatura se eleva a 0 C durante 30 min Antes de inyectar dióxido de carbono gaseoso la temperatura se devuelve a 78 C Después de inyección la solución se mantiene a esta temperatura durante otros 10 min y se coloca en NaOH (100 mL) Después se lava la solución con éter de etilo (2x100 mL) la capa acuosa se neutraliza y se extrae con DCM (3x100 mL) Las fases combinadas DCM se secan sobre sulfato de magnesio El crudo tiene suficiente pureza y es utilizado en la **Etapa B** sin ninguna purificación adicional LCMS m/z 398 41 (M+H)

Etapa B

La mezcla cruda (50 mg) de la Etapa A BOP (84 mg) y Hueni g base (67µL) se disuelven en THF (5 mL) La mezcla se agita durante 5 min antes se agrega metilamina (250 µL 2N en THF) Después de agitación durante 16 h la solución amarillenta se pone en agua (100 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación final sobre gel de sílice produce el compuesto del título LCMS m/z 411 41 (M+H)

EJEMPLO 17

Síntesis de 5-(6-ciclopropilmetoxi 2-etil piridin-3 il) 1-((S) 2-metoxi 1-metil etil)-3 6-dimetil 1H pirrolo[3 2 b]piridino



Etapa A

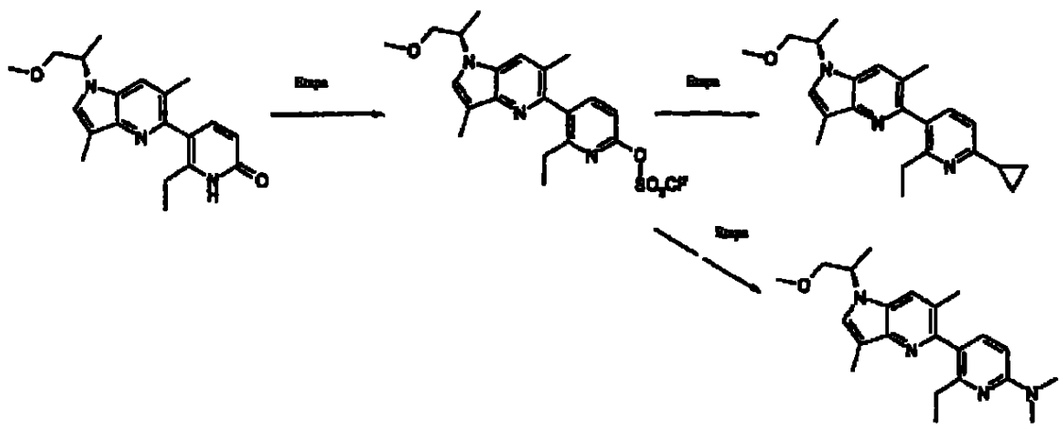
Se disuelve 5-(2 Etil-6 metoxi pindin 3 il) 1 ((S) 2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]pindino (5 00 g) en HCl 4N (150 mL) y se calienta a 75 C durante 7 días Una vez que el control TLC verifica principalmente el material hidrolizado se agregan NaOH 10N (60 0 mL) y bicarbonato de sodio saturado (200 mL) La extracción con DCM (3x200 mL) se seca sobre sulfato de magnesio y la purificación sobre gel de sílice produce la piridona LCMS m/z 340 06 (M+H)

Etapa B

Se disuelven la pindona (50 mg) de la Etapa C bromometilciclopropano (500 mg) y carbonato de potasio (500 mg) en DMF (3 0 mL) Después se agita durante la noche a ta la mezcla se pone en agua (100 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 394 16 (M+H)

EJEMPLO 18

Síntesis de 5-(6-ciclopropil 2-etil piridin-3 il) 1-((S) 2-metoxi 1-metil-etil)-3 6 dimetil 1H pirrolo[3 2-b]piridino y {6-etil-5 [1-((S) 2-metoxi 1-metil-etil)-3 6 dimetil 1H-pirrolo[3 2-b]pindin-5-il] piridin 2 il}-dimetil-amin



Etapa A

Se disuelven 6 Etil-5-[1 ((S) 2-metoxi 1 metil-etil) 3 6-dimetil-1H pirrolo[3 2 b]piridin-5 il] 1H piridin 2 ona (2 00 g) y trietilamina (2 05 mL) en DCM (100 mL) Después se enfría a 0 C se agrega anhídrido trifluorometanosulfónico y la reacción se agita durante 30 min a esta temperatura Posteriormente la mezcla amarillenta se pone en agua (200ml) se extrae con DCM (3x200 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el filtrado LCMS m/z 472 26 (M+H)

Etapa B

El filtrado (50 mg) de la Etapa A y ciclopropil ácido borónico (91 mg) se disuelven en tolueno (5 mL) Después se desgasifican durante 5 min se agrega tetrakis (trifenilfosfina) paladio (0) (12 mg) y la mezcla se desgasifica otra vez Se agrega una solución de carbonato de potasio (0 50 ml 2N) seguido por calentamiento a 110 C durante 16 h Posteriormente la mezcla se pone en agua (100 mL) se

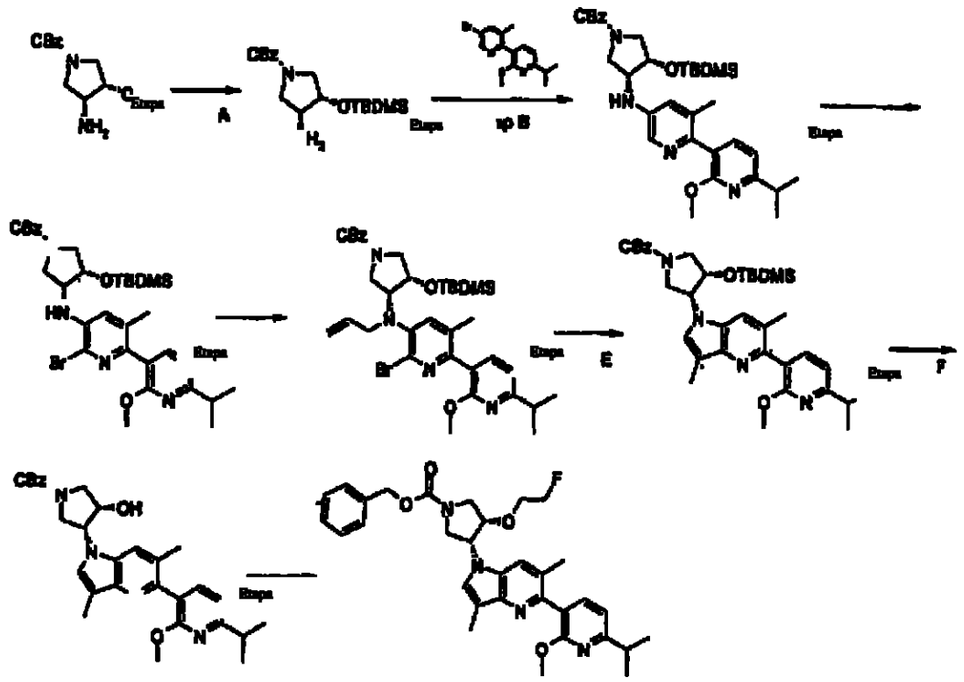
extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 364 45-(M+H)

Etapa C

El filtrado (100 mg) de la Etapa A se disuelve en a solución NMP 5N de dimetilamina (1 50 mL) y posteriormente se calienta a 80 C durante 8 h La mezcla de reacción se coloca entonces en agua (100 mL) se extrae con DCM (3x100 mL) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 367 43 (M+H)

EJEMPLO 19

Síntesis de éster de bencilo de ácido (3S 4R)-3-(2 fluoro-etoxi)-4-[5-(6 isopropil 2 metoxi-piridin-3 il)-3 6-dimetil-pirrolo[3 2 b]piridin 1 il] pirrolidin 1-carboxílico acid benzil éster



Etapa A

A una solución de éster de bencilo de ácido (3R 4S) 3-amino-4 hidroxi pirrolidino-1-carboxílico (3 g) en DCM (15 mL) se agrega imidazol (1 3 g) a 0 C Se agrega cloruro de *terc*-Butildimetilsilil (1 9 g) a la anterior solución a 0 C Después de agitar a 0 C durante 30 min el baño de hielo se remueve La mezcla se agita a TA durante 2 h y se vierte en EtOAc (200 mL) La mezcla se lava con agua y solución salina y se seca sobre $MgSO_4$ Después de remoción del solvente el residuo se purifica por cromatografía de columna flash para dar éster de bencilo de ácido (3R 4S) 3-amino-4-(terc-butil-dimetil silaniloxi) pirrolidino 1 carboxílico como aceite incoloro LCMS Rt 1 40 min m/z 351 07 (M+H)

Etapa B

A una solución de éster de bencilo de ácido (3R 4S) 3-amino-4 (terc-butil-dimetil silaniloxi) pirrolidino-1-carboxílico (3 g) y 5-bromo-6 isopropil 2 metoxi-3 metil-[2 3]bipiridinilo (3 02 g) en tolueno (20 mL) se agrega $Pd_2(dba)_3$ (0 313 g) BINAP (0 43 g) y NaOtBu (1 15 g) a ta La mezcla se agita a 80 C durante 22 h y se vierte en agua (150 mL) La mezcla se extrajo con EtOAc y los extractos combinados se lavan con solución salina Después se lleva sobre $MgSO_4$ el solvente se remueve bajo presión reducida El residuo se purifica por cromatografía de columna flash sobre gel de sílice para producir éster de bencilo de ácido (3S 4R)-3-(terc-butil-dimetil-silaniloxi)-4 (6 isopropil 2 metoxi 3-metil-[2 3]bipiridinil 5 ilamino)-pirrolidino 1 carboxílico como amorfo LCMS Rt 1 62 min m/z 591 15 (M+H)

Etapa C

A una solución agitada de éster de bencilo de ácido (3S 4R) 3 (terc-butil-dimetil silaniloxi)-4 (6 isopropil 2 metoxi 3 metil-[2 3']bipiridinil-5-ilamino) pirrolidino-1 carboxílico (4 07 g) en cloroformo (25 mL) se agrega NBS (1 23 g) a ta Después de agitación a TA durante 15 min el solvente se evapora bajo presión reducida y el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar éster de bencilo de ácido (3R 4S)-3-(6-bromo-6 isopropil 2 metoxi 3-metil [2 3]bipiridinil 5 ilamino)-4-(terc-butil-dimetil-silaniloxi) pirrolidino-1-carboxílico como amorfo incoloro Rf (hexano EtOAc = 2 1) = 0 55

Etapa D

A una solución agitada de éster de bencilo de ácido (3R 4S)-3-(6 bromo-6 isopropil 2 metoxi 3 metil [2 3]bipiridinil 5 ilamino)-4 (terc-butil-dimetil-silaniloxi) pirrolidino-1-carboxílico (4 03 g) en THF (25 mL) se agrega una solución de KOtBu en THF (2 41 ml 1 M) a ta Se agrega bromuro de alilo (2 04 mL) a la anterior solución durante 10 min a ta La mezcla se agita a TA durante 16 h y se vierte en agua La mezcla se extrajo con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de remoción del solvente bajo presión reducida el residuo se purifica por cromatografía de columna sobre gel de sílice para dar éster de bencilo de ácido (3R 4S)-3-[alil (6 bromo-6 isopropil 2 metoxi 3 metil [2 3]bipiridinil 5-il)-amino]-4 (terc-butil-dimetil-silaniloxi) pirrolidino-1 carboxílico como amorfo LCMS Rt 1 93 min m/z 709/711 (M+H)

Etapa E

A una solución de éster de bencilo de ácido (3R 4S) 3 [alil (6 bromo-6 isopropil 2 metoxi 3 metil [2 3']bipiridinil 5 il)-amino]-4 (terc-butil-dimetil-silaniloxi)-pirrolidino-1-carboxílico (3 2 g) en DMF (20 mL) se agrega $Pd(OAc)_2$ (81 mg) K_2CO_3 (1 87 g) y bromuro de tetrabutilamonio (1 6 g) a ta La mezcla se agita a 80 C durante 2 h y se vierte en agua La mezcla se extrajo con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de evaporación del solvente bajo presión reducida el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar éster de bencilo de ácido (3S 4R) 3-(terc-butil-dimetil-silaniloxi)-4 [5-(6 isopropil 2 metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] pirrolidino 1 carboxílico como amorfo LCMS Rt 1 62 min m/z 629 18 (M+H)

Etapa F

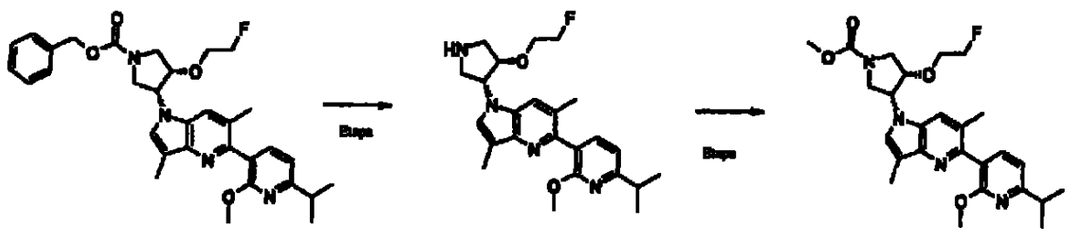
A una solución agitada de éster de bencilo de ácido (3S 4R)-3-(terc-butil-dimetil silaniloxi)-4-[5-(6-isopropil 2-metoxi piridin-3 il) 3 6-dimetil pirrolo[3 2-b]piridin 1 il] pirrolidino 1 carboxílico (2 3 g) en THF (14 mL) se agrega una solución de fluoruro de tetrabutilamonio en THF (4 8 ml 1M) a ta La mezcla se agita a TA durante 10 min y se vierte en agua helada (80 mL) La mezcla se extrajo con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de remoción del solvente bajo presión reducida el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar éster de bencilo de ácido (3S 4R)-3-hidroxi-4 [5-(6 isopropil 2 metoxi-piridin 3 il) 3 6-dimetil-pirrolo[3 2 b]piridin 1 il] pirrolidino 1-carboxílico como amorfo incoloro LCMS Rt 1 45 min m/z 515 10 (M+H)

Etapa G

A una solución de éster de bencilo de ácido (3S 4R) 3 hidroxi-4 [5-(6-isopropil 2 metoxi pindin-3 il)-3 6-dimetil pirrolo[3 2-b]pindin 1 il]-pirrolidino-1-carboxílico (1 88 g) en DMF (15 mL) se agrega hidruro de sodio (0 44 g) y bromofluoroetano (0 82 mL) a ta Después de agitación a TA durante 2 5 h la mezcla se vierte en agua helada y se extrae con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de evaporación del solvente bajo presión reducida el residuo se purifica por cromatografía de columna flash sobre gel de sílice para producir éster de bencilo de ácido (3S 4R) 3 (2 fluoro-etoxi)-4-[5-(6 isopropil 2 metoxi piridin 3 il) 3 6-dimetil-pirrolo[3 2 b]piridin 1 il] pirrolidino-1 carboxílico como amorfo incoloro LCMS Rt 1 49 min m/z 561 11 (M+H)

EJEMPLO 20

Síntesis de éster de metilo de ácido (3S 4R)-3-(2 fluoro-etoxi)-4-[5-(6 isopropil 2-metoxi piridin-3-il)-3 6-dimetil pirrolo[3 2-b]piridin 1-il]-pirrolidino 1-carboxílico



Etapa A

A una solución de éster de bencilo de ácido (3S 4R) 3 (2 fluoro-etoxi)-4-[5 (6 isopropil 2-metoxi pindin 3 il) 3 6-dimetil-pirrolo[3 2 b]pindin 1 il]-pirrolidino-1

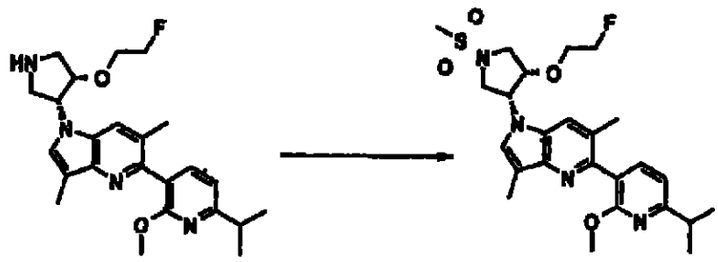
carboxílico (1 9 g) en EtOH (10 mL) se agrega 10 % Pd/C (0 3 g) a ta La suspensión se agita a TA bajo hidrógeno durante 14 h El catalítico se remueve por filtración y el filtrado se concentra bajo presión reducida El residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar 1-[(3R 4S)-4-(2 fluoro-etoxi)-pirrolidin 3 il] 5 (6 isopropil 2 metoxi pirídin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridino como amorfo incoloro LCMS Rt 1 29 min m/z 427 11 (M+H)

Etapa B

A una solución agitada de 1 [(3R 4S)-4 (2 fluoro-etoxi) pirrolidin 3 il] 5 (6-isopropil 2 metoxi pirídin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridino (0 1 g) en DCM (1 mL) se agrega cloroformato de metilo (0 03 mL) a ta Después de agitación a TA durante 15 min la reacción se apaga con Na_2CO_3 acuoso saturado (3 mL) La mezcla se extrajo con EtOAc Los extractos combinados se secan sobre $MgSO_4$ y se concentran bajo presión reducida El residuo se purifica por TLC preparativo para dar éster de metilo de ácido (3S 4R) 3 (2 fluoro-etoxi)-4 [5-(6 isopropil 2 metoxi pirídin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] pirrolidino-1 carboxílico como amorfo incoloro LCMS Rt 1 39 min m/z 485 13 (M+H)

EJEMPLO 21

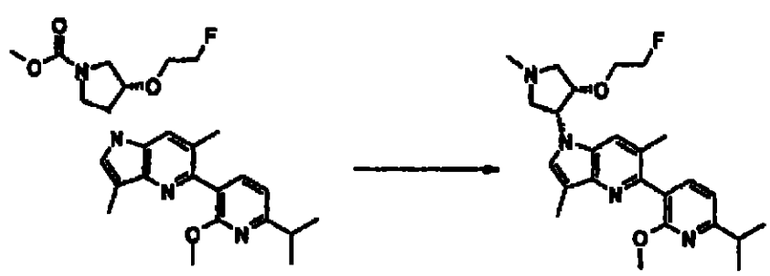
Síntesis de 1-[(3R 4S)-4-(2 fluoro-etoxi) 1-metanosulfonil pirrolidin-3 il]-5-(6 isopropil 2-metoxi piridin-3-il)-3 6-dimetil 1H-pirrolo[3 2-b]piridino



A una solución agitada de 1 [(3R 4S)-4 (2 fluoro-etoxi) pirrolidin 3-il] 5-(6-isopropil 2 metoxi-piridin-3-il) 3 6-dimetil 1H-pirrolo[3 2 b]piridina (0 1 g) en DCM (1 ml) se agrega cloruro de metanosulfonilo (0 03 ml) a temperatura ambiente Después de agitación a temperatura ambiente durante 15 min la reacción se apaga con Na_2CO_3 acuoso saturado (3 ml) La mezcla se extrae con EtOAc Los extractos combinados se secan sobre $MgSO_4$ y se concentran bajo presión reducida El residuo se purifica por TLC preparativo para dar 1 [(3R 4S)-4 (2 fluoro-etoxi) 1 metanosulfonil pirrolidin 3 il] 5 (6 isopropil 2 metoxi-piridin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridino como amorfo incoloro LCMS Rt 1 35 min m/z 505 10 (M+H)

EJEMPLO 22

Síntesis de 1 [(3R 4S)-4-(2 fluoro-etoxi) 1 metil-pirrolidin-3 il]-5-(6 isopropil 2 metoxi piridin-3 il)-3 6-dimetil 1H pirrolo[3 2 b]piridino

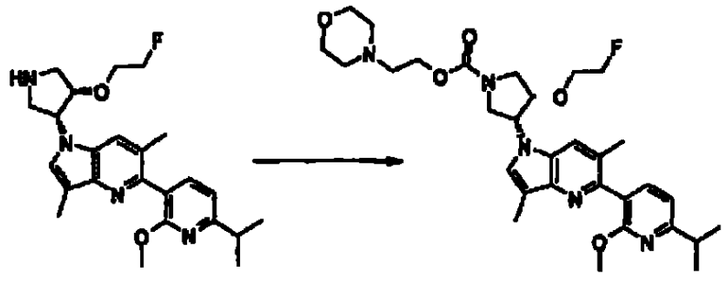


A una solución de éster de metilo de ácido (3S 4R) 3-(2 fluoro-etoxi)-4 [5 (6 isopropil 2 metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] pirrolidino-1

carboxílico (77 mg) en THF (1 ml) se agrega una solución de $LiAlH_4$ en THF (1 5 mL 1 M) a ta Después de agitación a TA durante 2 h la reacción se apaga con agua Las sales orgánicas se remueven por filtración de Celita Los filtrados se concentran bajo presión reducida y el residuo se purifica por cromatografía flash sobre gel de sílice para producir 1 [(3R 4S)-4 (2 fluoro-etoxi)-1-metil pirrolidin 3 il]-5 (6 isopropil 2-metoxi-pindin 3 il)-3 6-dimetil-1H pirrolo[3 2-b]pindino como amorfo incoloro LCMS Rt 1 24 min m/z 441 14 (M+H)

EJEMPLO 23

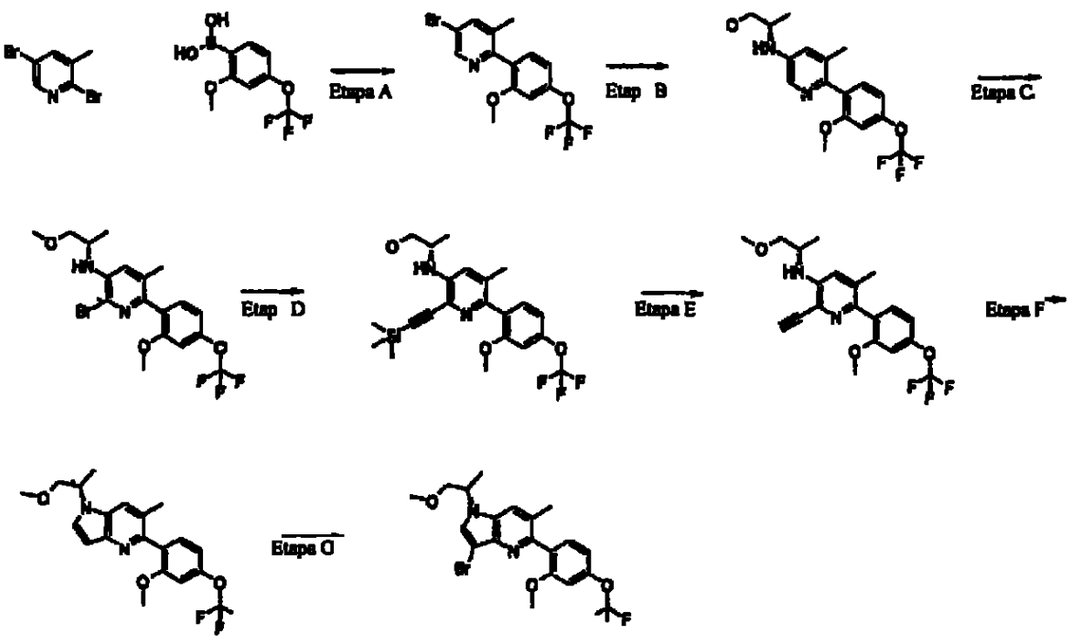
Síntesis de éster de 2 morfolin-4-il-etilo de ácido (3S 4R)-3-(2 fluoro-etoxi)-4 [5-(6-isopropil 2 metoxi piridin-3 il)-3 6-dimetil pirrolo[3 2-b]piridin 1 il] pirrolidino-1-carboxílico



A una solución agitada de 4 (2 hidroxietil) morfolino (0 063 ml) en DCM (1 ml) es 1 1 -carbonildiimidazol (84 mg) a ta Después de agitación a TA durante 30 min 1 [(3R 4S)-4-(2 fluoro-etoxi) pirrolidin 3 il] 5-(6 isopropil 2 metoxi pindin 3 il) 3 6 dimetil 1H pirrolo[3 2 b]pindino (0 2 g) se agrega a la mezcla Después de agitación a TA durante 1 día la mezcla se purifica por HPLC preparativo para dar éster de 2-morfolin-4-il-etilo de ácido (3S 4R) 3 (2 fluoro-etoxi)-4-[5 (6 isopropil 2 metoxi piridin-3-il)-3 6-dimetil pirrolo[3 2 b]pindin 1 il] pirrolidino-1 carboxílico como amorfo LCMS Rt 1 38 min m/z 584 (M+H)

EJEMPLO 24

Síntesis de 1-((S) 2-metoxi 1-metil-etil)-5-(2-metoxi-4 trifluorometoxi fenil)-6 metil 1H-pirrolo[3 2-b]piridino y 3-bromo 1-((S) 2-metoxi 1 metil-etil)-5-(2 metoxi-4-trifluorometoxi fenil)-6 metil 1H-pirrolo[3 2 b]piridino



Etapa A

A una solución de 2 5-dibromo 3-metil pindino (40 g) y ácido 2 metoxi-4-trifluorometoxi fenil borónico (39 5 g) en tolueno (200 ml) se agrega $Pd(Ph_3P)_4$ (5 5 g) y solución acuosa de K_2CO_3 2M (160 ml) a ta La mezcla se agita a 85 C durante 16 h La mezcla se vierte en agua y se extrae con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de evaporación del solvente el residuo se purifica por cromatografía de columna flash

sobre gel de sílice para dar 5 bromo-2 (2 metoxi-4 trifluorometoxi-fenil) 3 metil-piridino como un sólido blanco MS 362/364 (M+H)

Etapa B

A una solución de 5-bromo 2 (2 metoxi-4 trifluorometoxi fenil)-3-metil-piridino (1 04 g) en tolueno (20 ml) se agrega (S) 2 metoxi 1 metil-etilamina (0 28 g) $Pd_2(dba)_3$ (0 11 g) BINAP (0 14 g) y NaOtBu (0 39 g) La mezcla se agita a 80 C durante 15 horas La mezcla se vierte en agua y se extrae con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de remoción del solvente bajo presión reducida el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar ((S) 2 metoxi 1 metil etil) [6 (2 metoxi-4 trifluorometoxi fenil)-5 metil piridin 3 il] amina como amorfo Rf (hexano EtOAc = 2 1) = 0 3

Etapa C

A una solución de ((S)-2-metoxi-1 metil-etil) [6 (2-metoxi-4 trifluorometoxi fenil) 5-metil piridin 3-il]-amina (1 g) en cloroformo (5 ml) se agrega NBS (0 48 g) a ta Después de agitación a TA durante 5 min la mezcla se purifica directamente por cromatografía de columna flash sobre gel de sílice para dar [2 bromo-6-(2 metoxi-4-trifluorometoxi fenil) 5 metil piridin 3 il] ((S) 2 metoxi 1 metil-etil)-amina como sólido blanco

Rf (hexano EtOAc = 4 1) = 0 3

Etapa D

A una solución de [2 bromo-6-(2 metoxi-4 trifluorometoxi fenil) 5 metil piridin-3 il]-((S) 2 metoxi 1-metil-etil)-amina (0 2 g) en DMF (1 ml) se agrega etinil trimetil silano (0 08 ml) Et_3N (0 09 ml) $PdCl_2(Ph_3P)_2$ (6 mg) y CuI (1 mg) a TA La mezcla se agita a TA durante 14 h La mezcla se vierte en agua y se extrae con EtOAc Los extractos combinados se lavan con solución salina y se secan sobre $MgSO_4$ Después de evaporación del solvente el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar ((S) 2 betoxi 1 metil-etil) [6 (2-metoxi-4 trifluorometoxi-fenil) 5 metil 2 trimetilsilaniletinil piridin 3 il] amina como aceite incoloro LCMS Rt 1 74 min m/z 467 15 (M+H)

Etapa E

A una solución de ((S) 2 betoxi 1 metil-etil) [6-(2 metoxi-4 trifluorometoxi-fenil) 5-metil 2 trimetilsilaniletinil piridin 3 il]-amina (0 18 g) en THF (2 ml) se agrega una solución de nBu_4NF en THF (0 48 mL 1 M) a ta Después de agitación a TA durante 15 min se agrega EtOAc a la mezcla La solución se lava con agua y solución salina y se seca sobre $MgSO_4$ Después de remoción del solvente bajo presión reducida el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar [2-etinil-6 (2 metoxi-4 trifluorometoxi fenil) 5 metil piridin 3 il] ((S) 2 metoxi 1 metil-etil)-amina como aceite incoloro LCMS Rt 1 58 min m/z 395 09 (M+H)

Etapa F

A una solución de [2-etinil-6 (2 metoxi-4 trifluorometoxi fenil) 5 metil piridin 3 il]-((S) 2-metoxi 1-metil-etil)-amina (0 1 g) en NMP (3 ml) se agrega tBuOK (28 mg) a ta La mezcla se agita a 80 C durante 1h La mezcla se diluye con EtOAc y se

lava con agua y solución salina Después de secado sobre $MgSO_4$ el solvente se evapora El residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar 1 ((S) 2 metoxi-1 metil-etil) 5-(2 metoxi-4 trifluorometoxi-fenil)-6-metil 1H pirrolo[3 2 b]piridino como amorfo LCMS 1 30 min m/z 395 05 (M+H)

Etapa G

A una solución de 1 ((S) 2 metoxi-1 metil-etil) 5 (2-metoxi-4-trifluorometoxi fenil) 6 metil 1H pirrolo[3 2 b]piridino (65 mg) en cloroformo (2 ml) se agrega NBS (32 mg) La mezcla se agita a TA durante 30 min y se diluye con EtOAc La mezcla se lava con agua y solución salina y se secan sobre $MgSO_4$ Después de remoción del solvente bajo presión reducida el residuo se purifica por TLC preparativo para dar 3 bromo-1 ((S)-2-metoxi 1 metil-etil) 5 (2 metoxi-4 trifluorometoxi fenil)-6 metil 1H pirrolo[3 2 b]piridino como sólido blanco LCMS rt 1 54 min m/z 472 96/474 96 (M+H)

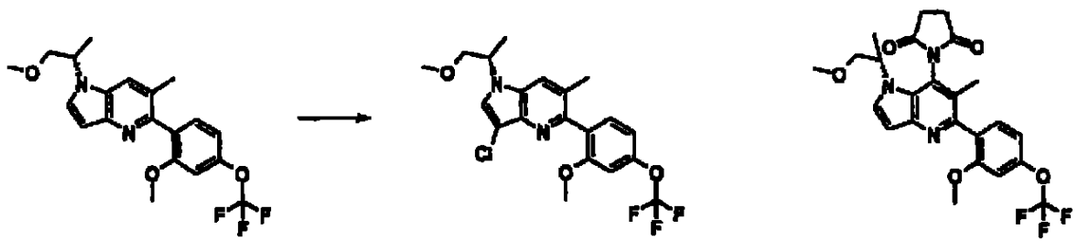
Al utilizar las etapas A F del Ejemplo 24 se preparan los siguientes compuestos análogamente

5-(6 isopropil 2 metoxi piridin-3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil-1H pirrolo[3 2 b]piridino (LCMS rt 1 40 min m/z 354 15 (M+H))

(R) 2 [5-(6-isopropil 2 metoxi pindin 3 il)-6 metil pirrolo[3 2 b]pindin 1 il] butan 1-ol (LCMS rt 1 39 min m/z 354 12 $(M+H)^+$)

EJEMPLO 25

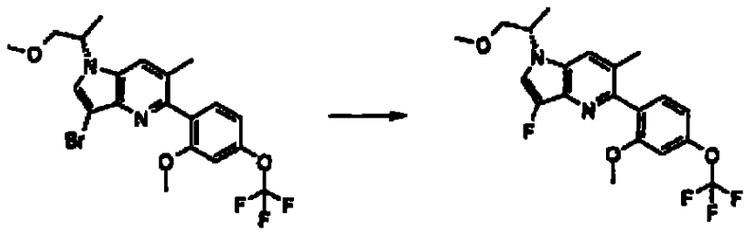
Síntesis de 3-cloro 1-((S) 2 metoxi 1-metil-etil)-5-(2 metoxi-4-trifluorometoxi fenil)-6-metil 1H pirrolo[3 2-b]piridino y 1 [1-((S) 2-metoxi 1-metil-etil)-5-(2 metoxi-4-trifluorometoxi fenil)-6-metil 1H pirrolo[3 2 b]piridin 7-il] pirrolidino 2 5-diona



A una solución de 1-((S) 2 metoxi-1 metil-etil) 5 (2 metoxi-4 trifluorometoxi fenil) 6-metil 1H pirrolo[3 2 b]pirídino (40 mg) en cloroformo (1 ml) se agrega NCS (15 mg) a ta Después de agitación a TA durante 15 h la mezcla se purifica directamente por TLC preparativo para dar 3-cloro-1 ((S)-2-metoxi 1-metil-etil) 5 (2 metoxi-4-trifluorometoxi fenil)-6-metil 1H pirrolo[3 2 b]pirídino (sólido blanco LCMS 1 53 min m/z 429 02/ 431 02 (M+H)) y 1 [1 ((S)-2-metoxi 1 metil-etil)-5 (2 metoxi-4 trifluorometoxi fenil)-6 metil-1H pirrolo[3 2 b]piridin 7 il] pirrolidino-2 5 diona (amorfo LCMS Rt 1 38 min m/z 492 09 (M+H))

EJEMPLO 26

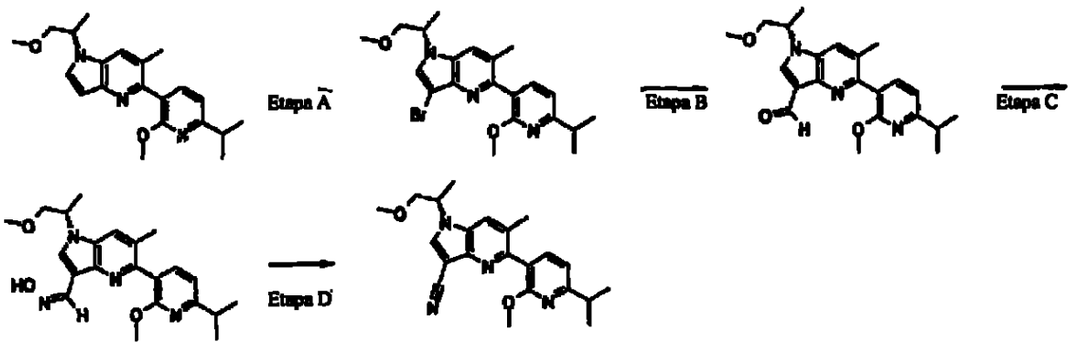
Síntesis de 3 fluoro 1-((S) 2 metoxi 1-metil-etil)-5-(2 metoxi-4 trifluorometoxi fenil)-6-metil 1H pirrolo[3 2-b]piridino



A una solución agitada de 3 bromo-1 ((S) 2-metoxi 1 metil-etil) 5 (2 metoxi-4-trifluorometoxi fenil)-6-metil 1H pirrolo[3 2 b]piridino (17 mg) en THF (1 ml) se agrega una solución de t BuLi en pentano (0 09 mL 1 7 M) a 78 C Después de agitar a la misma temperatura durante 1 h se agrega una solución de N fluorobenceno-sulfonimida (46 mg) en THF (1 ml) La mezcla se agita a 78 C durante 30 min y a 0 C durante 30 min La mezcla se vierte en agua y se extrae con EtOAc Los extractos combinados se secan sobre $MgSO_4$ y se concentran bajo presión reducida El residuo se purifica por TLC preparativo para dar 3 fluoro 1 ((S) 2 metoxi 1 metil-etil) 5 (2 metoxi-4-trifluorometoxi fenil)-6 metil 1H pirrolo[3 2 b]pindino como amorfo LCMS Rt 1 49 min m/z 413 02 (M+H)

EJEMPLO 27

Síntesis de 3 bromo-5-(6 isopropil 2-metoxi piridin-3 il) 1-((S) 2 metoxi 1 metil-etil)-6-metil 1H pirrolo[3 2-b]piridino y 5-(6 isopropil 2-metoxi-piridin-3 il) 1-((S) 2-metoxi 1-metil-etil)-6-metil 1H pirrolo[3 2 b]pindino-3-carbonitrilo



Etapa A

A una solución de 5 (6 isopropil 2 metoxi pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]pirdino (1 25 g) en cloroformo (10 ml) se agrega NBS (0 66 g) a 0 C La mezcla se agita a TA durante 2 h y se diluye con DCM La mezcla se lava con agua y solución salina Después de secado sobre $MgSO_4$ el solvente se *remueve bajo presión reducida* El *residuo se purifica por cromatografía* de columna flash sobre gel de sílice para dar 3-bromo-5 (6 isopropil 2 metoxi pirdin 3 il) 1 ((S) 2-metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]pirdino como cristal blanco LCMS Rt 1 59 min m/z 432/434 (M+H)

Etapa B

A una solución de 3 bromo-5 (6 isopropil-2 metoxi-pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]pirdino (4 g) en THF (4 ml) se trata con n BuLi en hexano (0 44 mL 1 6 M) a 70 C Después de agitar a 70 C durante 40 min DMF (0 11 ml) se agrega a la mezcla La mezcla se agita a 70 C durante 90 min La reacción se apaga con agua y la mezcla se extrae con EtOAc El extracto se seca sobre $MgSO_4$ y se concentra bajo presión reducida El residuo se purifica por TLC preparativo para dar 5 (6-isopropil 2 metoxi pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]pirdino-3-carbaldehido como amorfo incoloro LCMS Rt 1 50 min m/z 382 20 (M+H)

Etapa C

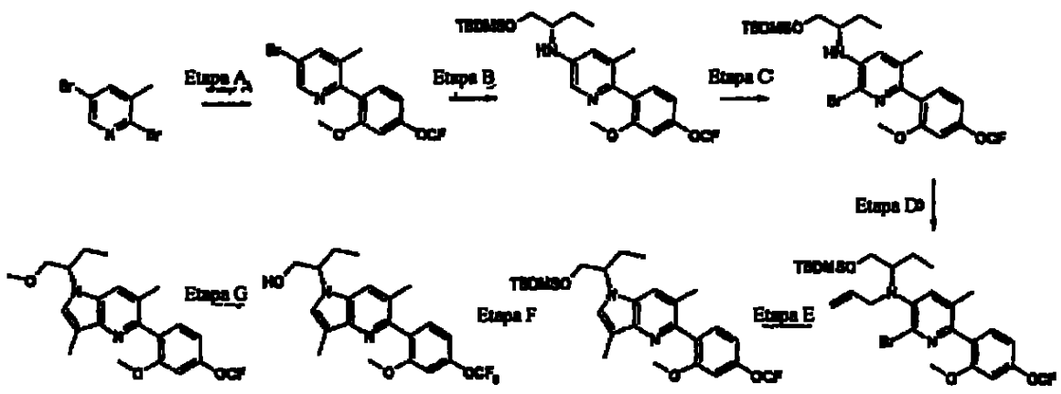
A una solución agitada de 5 (6 isopropil 2 metoxi pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]piridino-3-carbaldehido (0 13 g) en DCM (3 ml) se agrega clorhidrato de hidroxilamina (36 mg) y Et_3N (0 07 ml) a ta La mezcla se agita a TA durante 2 h y se diluye con EtOAc La mezcla se lava con agua y se seca sobre $MgSO_4$ El solvente se remueve bajo presión reducida para dar 5-(6 isopropil 2-metoxi pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6-metil 1H-pirrolo[3 2 b]piridino-3-carbaldehido oxima como una mezcla de sin y anti-isómeros LCMS Rt 1 38 min m/z 397 21 (M+H) y Rt 1 44 min m/z 397 21 (M+H)

Etapa D

A una solución de 5 (6-isopropil-2 metoxi pirdin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]piridino-3-carbaldehido oxima (0 136 g) en DCM (3 ml) se agrega Et_3N (0 47 ml) y cloruro de metanosulfonilo (0 13 ml) a ta Después de agitación a TA durante 15 h la mezcla se vierte en agua (30 ml) y se extrae con EtOAc El extracto se lava con agua y solución salina y se seca sobre $MgSO_4$ Después de evaporación del solvente el residuo se purifica por cromatografía de columna flash sobre gel de sílice para dar 5 (6-isopropil 2 metoxi-pirdin-3-il) 1 ((S) 2-metoxi-1 metil-etil)-6 metil 1H pirrolo[3 2 b]piridino-3-carbonitrilo como amorfo LCMS Rt 1 59 min m/z 379 19 (M+H)

EJEMPLO 28

Síntesis de (S) 2 [5-(2-metoxi-4-trifluorometoxi fenil) 3 6-dimetil-pirrolo[3 2 b]piridin 1-il] butan 1-ol y 1-((S) 1-metoximetil propil)-5-(2-metoxi-4 trifluorometoxi fenil)-3 6-dimetil 1H pirrolo[3 2 b]piridino



Etapa A

Una mezcla de 2 5-dibromo-3-metil piridino (40g) ácido 2 metoxi-4 trifluorometoxi 1 fenilborónico (39 5g) y K_2CO_3 2M (159 ml) en tolueno (300 ml) se desgasifica con N_2 durante 2 min seguido por adición de $Pd(PPh_3)_4$ (5 5g) La mezcla resultante se agita a 85 C bajo N_2 durante la noche Después que se completa la reacción la mezcla se vierte en agua (300 mol) y se extrae con acetato de etilo (3x150 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto 5-bromo 2-(2 metoxi-4-trifluorometoxi fenil) 3 metil piridino se obtiene después de cromatografía flash (Hexano/EtOAc=20/1) TLC Rf 0 35 (Hexano/EtOAc=4/1)

Etapa B

Una mezcla de 5 bromo 2 (2 metoxi-4 trifluorometoxi fenil)-3-metil piridino (1 31 g) (S) 1 (*terc*-Butil-dimetil silaniloximetil) propilamina (885 mg) (+/) BINAP (181 mg) y NaOBut (488 mg) en tolueno (10 ml) se desgasifica con N_2 durante 2 min seguido por adición de $Pd_2(dba)$ (133 mg) La mezcla resultante se agita a 70 C bajo N_2 durante 20 h La mezcla se vierte en agua y se extrae con EtOAc (3x30 ml) Las capas orgánicas combinadas se lavan con solución salina se secan

sobre Na_2SO_4 y se evaporan El producto crudo se purifica por cromatografía flash (Hexano/EtOAc=3/1) m/z 485 5 (M+H)

Etapa C

257 mg de [(S) 1 (*terc*-Butil-dimetil-silaniloximetil) propil] [6-(2 metoxi-4 trifluorometoxi fenil) 5 metil-piridin 3-il] amina se disuelve en $CHCl_3$ (6 ml) y NBS (95 mg) se agrega a temperatura ambiente Después de agitar a temperatura ambiente durante 10 min la mezcla se diluye con $CHCl_3$ y se lava con H_2O solución salina y se secan sobre Na_2SO_4 El producto puro 2 bromo-6 (2 metoxi-4-trifluorometoxi fenil) 5-metil-piridin 3-il]-[(S) 1-(terc-butil-dimetil silaniloximetil) propil]-amina se obtiene después de cromatografía de columna (Hexano/EtOAc=8/1) MS m/z 563 3/565 3 (M+H)

Etapa D

2 Bromo-6-(2 metoxi-4 trifluorometoxi fenil)-5 metil piridin 3 il] [(S) 1-(terc-butil dimetil silaniloximetil) propil]-amina (230 mg) en THF anhidro (6 ml) se agrega $KOBu^t$ 1M (1 03 ml) seguido por bromuro de alilo (71µl) a temperatura ambiente y la mezcla resultante se le permite agitarse a temperatura ambiente durante 20 h La reacción se apaga al agregar 10 ml H_2O y la mezcla se extrae con EtOAc (3x15 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan La cromatografía de columna Flash (Hexano/EtOAc=15/1) da el producto deseado TLC Rf 0 55 (Hexano/EtOAc=10/1)

Etapa E

315

A una mezcla de alil [2 bromo-6-(2 metoxi-4 trifluorometoxi fenil) 5-metil pirdin 3-il] [(S) 1 (terc-butil-dimetil-silaniloximetil) propil]-amina (1 0 g) bromuro de tetrabutilamonio (589 mg) K_2CO_3 (687 mg) en DMF (40 ml) se desgasifica con N_2 durante 3 min seguido por adición de $Pd(OAc))_2$ (37 mg) La mezcla resultante se agita a 80 C durante 18 h La mezcla de reacción se vierte en agua y se extrae con EtOAc (3x25 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto crudo se purifica por cromatografía flash (Hexano/EtOAc=10/1) MS m/z 523 5 (M+H)

Etapa F

1 [(S) 1 (terc-Butil-dimetil silaniloximetil) propil] 5 (2 metoxi-4-trifluorometoxi fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridino (1 19g) en THF (30 ml) se agrega fluoruro de tetrabutilamonio (715 mg) y la mezcla se le permitió agitarse a temperatura ambiente durante 30 min Después que la reacción se completa el solvente se remueve y la mezcla cruda se purifica por cromatografía flash (CH_2Cl_2/MeOH=5/1) para dar el producto deseado LC MS m/z 409 01 (M+H)

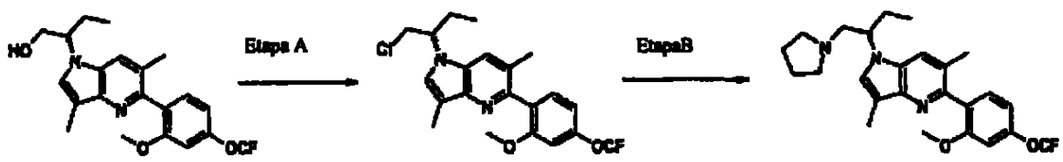
Etapa G

(S) 2 [5 (2-metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2-b]pirdin 1 il] butan 1-ol (60 mg) en THF anhidro (5 ml) se agrega NaH al 60% (29 mg) y la mezcla se le permitió agitarse a temperatura ambiente durante 10 min antes se agrega MeI (46µl) Después de agitar a temperatura ambiente durante 1 h la reacción se apaga al agregar agua (15 ml) La mezcla se extrae con EtOAc (3x25 ml) se seca sobre Na_2SO_4 y se evapora El producto puro 1 ((S) 1 metoximetil-propil) 5 (2

metoxi-4-trifluorometoxi fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridino se obtuvo por cromatografía de columna flash (Hexano/EtOAc=3/1) LC MS m/z 423 03 (M+H)

Ejemplo 29

Síntesis de 1-((S) 1-clorometil-propil)-5-(2 metoxi-4-trifluorometoxi fenil)-3 6 dimetil 1H pirrolo[3 2 b]piridino y 5-(2-metoxi-4-trifluorometoxi fenil)-3 6 dimetil 1-((S) 1 pirrolidin 1-ilmetil-propil) 1H pirrolo[3 2 b]piridino



Etapa A

(S) 2 [5 (2 Metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butan 1-ol (330 mg) en $ClCH_2CH_2Cl$ (20 ml) se enfría a 0 C y se agrega $SOCl_2$ (1 77 ml) en forma de gotas A la reacción se le permite agitarse a temperatura ambiente durante 12 h Después de remoción del solvente el producto crudo se purifica por columna flash (Hexano/EtOAc=3/1) MS m/z 427 4 (M+H)

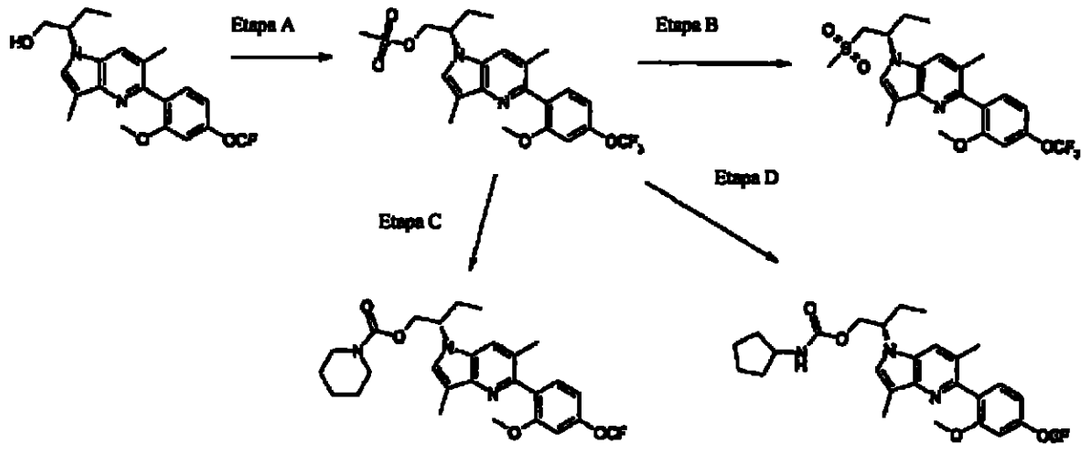
Etapa B

Una mezcla de 1 ((S)-1-clorometil propil) 5 (2 metoxi-4-trifluorometoxi fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridino (55 mg) KI (15 mg) y pirrolidino 0 8 ml en DMSO (4 ml) se calienta a 120 C durante 19 h Después de agitar el material desaparece la mezcla se vierte en agua y se extrae con CH_2Cl_2 (3x20 ml) Las

capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro 5 (2 metoxi-4 trifluorometoxi-fenil) 3 6-dimetil 1 ((S) 1 pirrolidin 1 ilmetil-propil) 1H pirrolo[3 2 b]pirdino se obtiene por purificación preparativa por TLC (CH_2Cl_2/MeOH=15/1) LC MS m/z 462 10-(M+H)

EJEMPLO 30

Síntesis de éster de (S) 2 [5-(2-metoxi-4 trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1-il]-butilo de ácido metanosulfónico 1-((S) 1 metanosulfonilmetil-propil)-5-(2-metoxi-4 trifluorometoxi fenil)-3 6-dimetil 1H pirrolo[3 2 b]piridino éster de (S) 2-[5-(2 metoxi-4-trifluorometoxi fenil)-3 6 dimetil-pirrolo[3 2-b]piridin 1-il] butilo de ácido piperidino 1-carboxílico y éster de (S) 2 [5-(2-metoxi-4-trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido ciclopentil-carbámico



Etapa A

(S) 2 [5 (2 Metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il]-butan 1-ol (120 mg) en CH_2Cl_2 (6ml) se enfría a 0° C y a la mezcla se agrega trietilamina

(82µl) seguido por cloruro de metanosulfonilo (45µl) A la mezcla se le permite agitarse a 0 C a temperatura ambiente durante 16 h Después de remoción del solvente la mezcla cruda se purifica por cromatografía de columna (CH_2Cl_2/MeOH=12/1) LC MS m/z 486 99 (M+H)

Etapa B

Una mezcla de éster (S) 2 [5 (2-metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido metanosulfónico (39 mg) KI (5 mg) y CH_3SO_2Na (100 mg) en DMSO (2 ml) se calienta a 80 C durante 17 h La mezcla se vierte en agua y se extrae con EtOAc (3x15 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro 1 ((S) 1 metanosulfonilmetil propil) 5 (2 metoxi-4 trifluorometoxi fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridino se obtuvo por purificación preparativa por TLC (Hexano/EtOAc=1/1) LC MS m/z 471 03 (M+H)

Etapa C

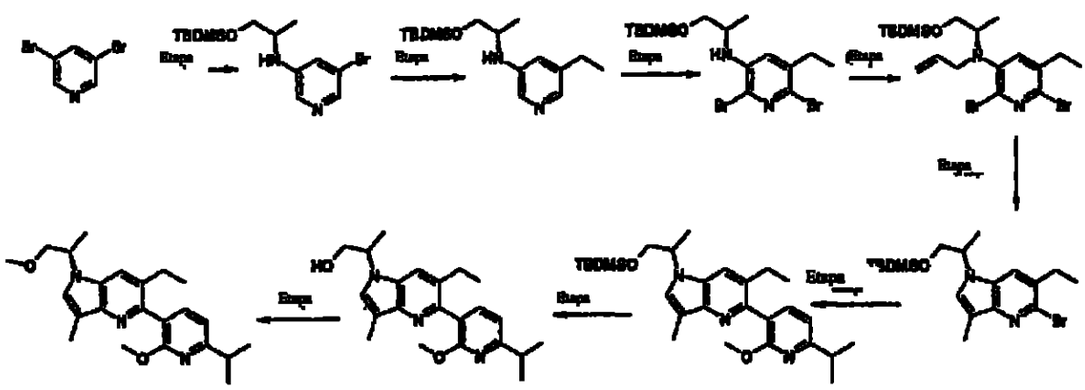
2 mL de éster de (S) 2 [5 (2 metoxi-4-trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido metanosulfónico (0 02 M en DMSO) se agrega 0 2 mL de piperidino (0 2 M en tolueno) seguido por $NaHCO_3$ (50 mg) y KI (10 mg) La mezcla resultante se agita a 80 C durante 18 h La mezcla se diluye con agua se extrae con EtOAc (2x10 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro éster de (S) 2-[5-(2 metoxi-4-trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido piperidino 1-carboxílico se obtuvo por purificación preparativa por TLC (Hexano/EtOAc=1/l) LC MS m/z 520 11 (M+H)

Etapa D

2 mL de éster de (S) 2 [5-(2 metoxi-4-trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]pindin 1 il] butilo de ácido metanosulfónico (0 02 M en DMSO) se agrega 0 2 mL de ciclopentilamina (0 2 M en tolueno) seguido por $NaHCO_3$ (50 mg) y KI (10 mg) La mezcla resultante se agita a 80 C durante 18 h La mezcla se diluye con agua se extrae con EtOAc (2x10 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro éster de (S) 2-[5-(2 metoxi-4-trifluorometoxi fenil) 3 6-dimetil-pirrolo[3 2 b]pindin 1 il] butilo de ácido ciclopentil-carbámico se obtiene por purificación preparativa por TLC (Hexano/EtOAc=1/1) LC MS m/z 520 12 (M+H)

EJEMPLO 31

Síntesis de (R) 2 [6-etil-5-(6 isopropil 2 metoxi-pirídin-3 il)-3 metil-pirrolo[3 2 b]pirídin 1-il] propan 1-ol y 6-etil-5-(6 isopropil 2-metoxi pirídin-3-il) 1-((R) 2 metoxi 1 metil-etil)-3-metil 1H-pirrolo[3 2-b]piridino



Etapa A

Una mezcla de 3 5-dibromopiridino (30 3g) (R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etilamina (25 4g) (+/) BINAP (6 37g) y $NaOBu^t$ (17 18g) en tolueno (300 ml) se desgasifica durante 5 min seguido por adición de $Pd_2(dba)_3$ (4 68g) La mezcla resultante se agita a 70 C durante 4 h La mezcla de reacción se vierte en agua (200 ml) se extrae con EtOAc (3x150 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto deseado se obtiene después de cromatografía de columna flash (Hexano/EtOAc=3/1) LC MS m/z 347 24 (M+H)

Etapa B

Una mezcla de (5 bromo piridin 3 il) [(R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etil] amina (22 74g) K_2CO_3 2M (99 ml) y 165 ml Et3B (1M en hexano) en tolueno (200 ml) se desgasifica con N_2 durante 5 min seguido por adición de $Pd(PPh_3)_4$ (3 8g) La mezcla resultante se le permite agitarse a 110 C durante 16 h La mezcla se vierte en agua (200 ml) se extrae con EtOAc (3x200 ml) se secan sobre Na_2SO_4 y se evaporan El producto crudo [(R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etil] (5 etil piridin 3-il)-amina se utiliza para la siguiente etapa sin purificación adicional LC MS m/z 295 14 (M+H)

Etapa C

El producto crudo de la última etapa se disuelve en $CHCl_3$ (250 ml) y NBS (2 eq) se agrega en una porción a temperatura ambiente Después de agitar a temperatura ambiente durante 15 min la solución se lava con agua (2x100 ml) La

fase orgánica se seca sobre Na_2SO_4 y se evapora El producto crudo se purifica por cromatografía flash (Hexano/EtOAc=811) LC MS m/z 451 12/453 11 (M+H)

Etapa D

(R)-2 (terc-Butil-dimetil-silaniloxi) 1 metil-etil] (2 6-dibromo-5-etil piridin 3 il)-amina (11 5g) en THF anhidro (180 ml) se agrega $KOBu^t$ 1M (50 9 ml) seguido por yoduro de alilo (3 48 ml) La mezcla resultante se le permite agitarse a temperatura ambiente durante 22 h antes que este se apague con agua (100 ml) La mezcla se extrae con EtOAc (3x150 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro alil [(R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etil] (2 6-dibromo-5-etil piridin 3 il) amina se obtiene después de cromatografía de columna (Hexano/EtOAc=10/1) TLC Rf 0 6 (Hexano/EtOAc=1011)

Etapa E

Una mezcla de alil-[(R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etil] (2 6-dibromo-5 etil piridin 3 il)-amina (8 3g) bromuro de tetrabutilamonio (6 0g) K_2CO_3 (6 99g) en DMF (100 ml) se desgasifica durante 3 min seguido por adición de $Pd(OAc))_2$ La mezcla resultante se agita a 80 C durante 18 h Después que la mezcla se completa la mezcla se vierte en H_2O (200 ml) se extrae con EtOAc (3x100 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto crudo se purifica por cromatografía de columna flash (Hexano/EtOAc=10/1) TLC Rf 0 5 (Hexano/EtOAc=4/1)

Etapa F

Una mezcla de 5-bromo-1 [(R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etil]-6-etil 3 metil 1H pirrolo[3 2-b]piridino (2 21g) K_2CO_3 2M (5 4 ml) y ácido 2 metoxi-6 isopropil-3 piridilborónico (1 20g) en DME (25 ml) se desgasifica con N_2 durante 2 min seguido por adición de $Pd(PPh_3)_4$ La mezcla resultante se agita a 85 C durante 16 h antes esta se vierte en agua (80 ml) y se extrae con EtOAc (3x30 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan La cromatografía de columna flash (Hexano/EtOAc=6/1) da el producto puro 1 [(R) 2 (terc-butil-dimetil silaniloxi) 1 metil-etil]-6-etil 5 (6 isopropil 2 metoxi piridin 3 il) 3-metil 1H pirrolo[3 2 b]piridino LC MS m/z 482 18 (M+H)

Etapa G

1-[(R)-2 (terc-Butil-dimetil silaniloxi) 1 metil-etil]-6-etil 5 (6-isopropil 2 metoxi piridin 3-il) 3 metil IH pirrolo[3 2 b]piridino (1 87g) en THF (60 ml) se agrega fluoruro de tetrabutilamonio (1 53g) y la mezcla se le permitió agitarse a temperatura ambiente durante 15 min antes que el solvente se evapore El producto crudo se purifica por cromatografía flash (Hexano/EtOAc=1/1) MS m/z 368 4 (M+H)

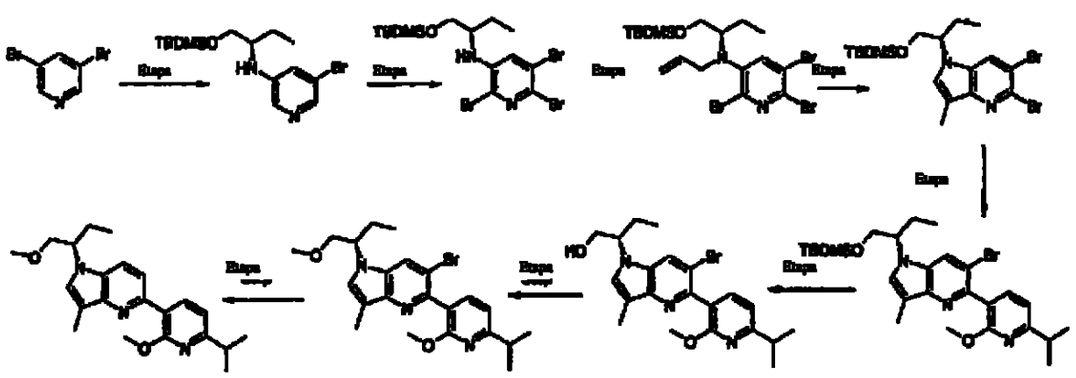
Etapa H

(R) 2 [6 Etil 5 (6-isopropil 2 metoxi piridin 3 il) 3 metil pirrolo[3 2 b]piridin 1 il] propan 1-ol (1 15g) en THF anhidro (40 ml) se agrega NaH (627 mg) y la mezcla se agita a temperatura ambiente durante 5 min antes de agregar MeI (978µl) La mezcla de reacción se agita a temperatura ambiente durante 3 h y luego se apaga

con H_2O (50 ml) y se extrae con EtOAc (3x40 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro 6-etil 5 (6 isopropil 2 metoxi-piridin 3 il) 1 ((R) 2 metoxi 1 metil etil) 3-metil-1H pirrolo[3 2-b] pindino se obtuvo por cromatografía flash (Hexano/EtOAc=4/1) LC MS m/z 382 44 (M+H)

EJEMPLO 32

Síntesis de (S) 2 [6 bromo-5-(6 isopropil 2-metoxi-piridin-3 il)-3-metil pirrolo[3 2 b]piridin 1 il] butan 1-ol 6-bromo-5-(6-isopropil 2-metoxi piridin-3 i) 1-((S) 1 metoximetil propil)-3-metil 1H-pirrolo[3 2 b]piridino y 5-(6 isopropil 2-metoxi piridin-3 il) 1-((S) 2-metoxi 1-metil-propil)-3-metil 1H pirrolo[3 2 b]piridino



Etapa A

Una mezcla de 3 5-dibromopiridino (50g) (S) 1-(terc-butil-dimetil-silaniloximetil) propilamina (43 68g) (+/) BINAP (10 51g) y NaOBu (28 35g) en tolueno (400 ml) se desgasifica con N_2 durante 5 min seguido por adición de $Pd_2(dba)_3$ (7 73g) La mezcla resultante se agita a 70 C durante 23 h La mezcla de reacción se vierte

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en agua (200 ml) se extrae con EtOAc (3x200 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto deseado se obtiene después de cromatografía de columna flash (Hexano/EtOAc=5/1) TLC Rf0 4 (Hexano/EtOAc=4/1)

Etapa B

(5-Bromo-pirdin-3-il) [(S) 1 (terc-butil-dimetil-silaniloximetil) propil]-amina (7 58g) en $CHCl_3$ (150 ml) se agrega NBS (7 51g) y la mezcla se agita a temperatura ambiente durante 15 min antes este se lava con H_2O (2x50 ml) La capa orgánica se seca sobre Na_2SO_2 y se evapora El producto crudo se purifica por cromatografía de columna (Hexano/EtOAc=10/1) TLC Rf 0 7 (Hexano/EtOAc=4/1)

Etapa C

(S) 1 (terc-Butil-dimetil-silaniloximetil) propil] (2 5 6 tribromo-pirdin 3-il)-amina (6 33g) en THF (60ml) se agrega 24 5 ml $KOBu^t$ (1 M en THF) seguido por yoduro de alilo (1 68 ml) La mezcla resultante se agita a temperatura ambiente durante 24 h antes esta se apaga con agua (60 ml) La mezcla se extrae con EtOAc (3x30 ml) y las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro alil [(S) 1 (terc-butil-dimetil silaniloximetil)-propil] (2 5 6 tribromo-pirdin 3 il) amina se obtuvo por cromatografía de columna flash (Hexano/EtOAc=15/1) TLC Rf 0 6 (Hexano/EtOAc=10/1)

Etapa D

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Una mezcla de alil-[(S) 1 (terc-butil-dimetil-silaniloximetil) propil] (2 5 6 tribromo-piridin 3-il)-amina (5 81g) bromuro de tetrabutilamonio (3 7g) K_2CO_3 (4 32g) en DMF (25 ml) se desgasifica con N_2 durante 2 min seguido por adición de $Pd(OAc))_2$ (214 mg) La mezcla resultante se agita a 80 C durante 1 5 h antes se vierte en agua (50 ml) y se extrae con EtOAc (3x30 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto crudo se purifica por cromatografía de columna flash (Hexano/EtOAc=10/1) TLC Rf 0 3 (Hexano/EtOAc=10/1)

Etapa E

Una mezcla de 5 6-dibromo-1 [(S) 1 (terc-butil-dimetil-silaniloximetil) propil] 3 metil 1H pirrolo[3 2 b]piridino (3 66g) K_2CO_3 2M (22 ml) ácido 2-metoxi-6 isopropil-3 piridilborónico (1 64g) en DME se desgasifica con N_2 durante 5 min seguido por adición de $Pd(PPh_3)_4$ (444 mg) La mezcla resultante se le permite agitarse a 85 C durante 3 5 h antes este se vierte en H_2O (50 ml) se extrae con EtOAc (3x40 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro 6-bromo 1 [(S) 1 (terc-butil-dimetil silaniloximetil) propil]-5-(6 isopropil 2 metoxi piridin 3 il) 3 metil 1H pirrolo[3 2-b]piridino se obtiene por cromatografía de columna flash (Hexano/EtOAc=8/1) LC MS m/z 547 3 (M+H)

Etapa F

6-Bromo 1 [(S) 1 (terc-butil-dimetil-silaniloximetil)-propil] 5 (6 isopropil 2 metoxi pridin 3 il) 3 metil 1H pirrolo[3 2 b]pridino (2 74g) en THF (50 ml) se agrega

fluoruro de tetrabutilamonio (1 97g) y la mezcla resultante se agita a temperatura ambiente durante 2h Después de remoción del solvente el producto crudo se purifica por cromatografía de columna (Hexano/EtOAc=1/1) LC MS m/z 433 35 (M+H)

Etapa G

Una mezcla de (S) 2 [6 bromo-5-(6-isopropil 2 metoxi piridin 3-il) 3-metil pirrolo[3 2 b]piridin 1 il] butan 1-ol (2 0g) en THF (40 ml) se agrega NaH al 60% (463 mg) y la mezcla se agita a 0 C durante 10 min antes se agrega MeI (578µl) Después de agitar a temperatura ambiente durante 3 5 h la mezcla se vierte en agua (50 ml) y se extrae con EtOAc (3x30 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan La cromatografía de columna (Hexano/EtOAc=6/1) da el producto puro 6 bromo-5 (6-isopropil-2 metoxi piridin 3-il) 1 ((S) 1-metoximetil propil) 3 metil 1H pirrolo[3 2 b]pirdino LC MS m/z 447 37 (M+H)

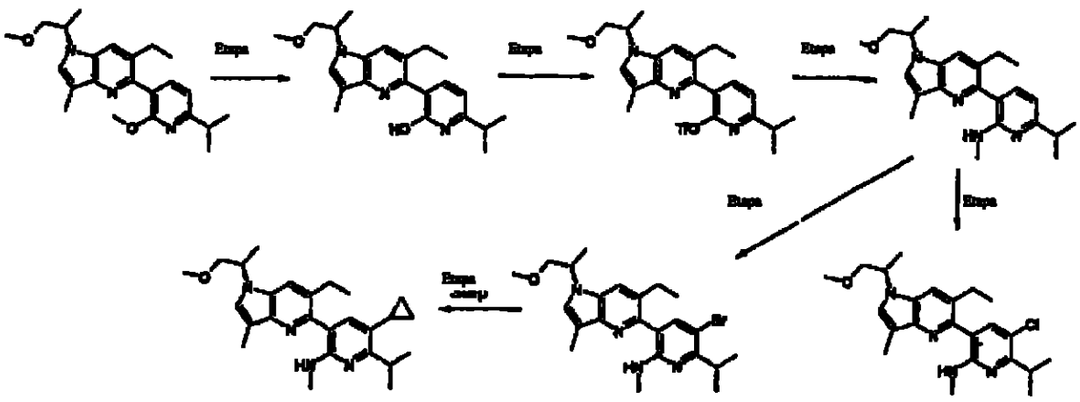
Etapa H

6 Bromo-5 (6-isopropil-2 metoxi piridin 3 il) 1 ((S) 1 metoximetil propil)-3-metil lH pirrolo[3 2 b]pirdino (450 mg) en EtOH (30 ml) se agrega 10% Pd/C (200 mg) bajo N_2 y la mezcla se agita bajo 40 psi H_2 presión durante 48 h el catalizador se remueve al filtrar a través de celita Después de remoción de solvente se obtuvo el producto deseado 5 (6 isopropil 2 metoxi piridin-3-il) 1 ((S) 2 metoxi 1 metil propil) 3 metil 1H pirrolo[3 2-b]pirdino MS m/z 368 4 (M+H)

EJEMPL 33

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Síntesis de {3-[6-etil 1-((R) 2-metoxi 1-metil-etil)-3-metil 1H pirrolo[3 2 b]piridin-5 il]-6-isopropil piridin 2 il}-metil-amina 5-cloro-3-[6-etil 1-((R) 2 metoxi 1-metil-etil)-3-metil 1H-pirrolo[3 2 b]piridin-5-il] 6-isopropil-piridin 2 il}-metil-amina {5-bromo-3-[6-etil 1-((R) 2-metoxi 1-metil-etil)-3 metil 1H pirrolo[3 2 b]piridin-5-il]-6-isopropil-piridin 2 il}-metil-amina y {5-ciclopropil 3 [6-etil 1-((R) 2-metoxi 1-metil-etil)-3 metil 1H pirrolo[3 2-b]piridin-5-il]-6 isopropil-piridin 2 il}metil-amina



Etapa A

Una mezcla de 6-etil 5 (6 isopropil 2 metoxi piridin 3 il) 1 ((R) 2 metoxi 1 metil etil) 3-metil 1H-pirrolo[3 2-b]piridino (1 02g) y HCl 6N (20 ml) se calienta a 75 C durante 20 h La mezcla se enfría a 0 C y se neutraliza con NaOH 10 N a PH>10 La solución básica se extrae con CH_2Cl_2 (3x40 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto crudo 3-[6-etil 1-((R) 2 metoxi 1 metil-etil)-3-metil 1H pirrolo[3 2 b]piridin 5 il]-6-isopropil-piridin 2-ol se utiliza para la siguiente etapa sin purificación adicional TLC Rf 0 2 (CH_2Cl_2/MeOH=12/1)

Etapa B

El producto crudo de la etapa previa se disuelve en CH_2Cl_2 (30 ml) y la mezcla se enfría a 0 C seguido por adición de trietilamina (1 11 ml) y anhídrido trifluorometanosulfónico (898 µl) Después de agitar a temperatura ambiente durante 3 h la mezcla se vierte en H_2O (30 ml) y se extrae con EtOAc (3x30 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro deseado éster de 3-[6-etil 1 ((R) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin-5 il]-6 isopropil piridin 2 ilo de ácido trifluoro-metanosulfónico se obtuvo por cromatografía de columna flash (CH_2Cl_2/MeOH=6/1) TLC Rf 0 4 (CH_2Cl_2/MeOH=12/1)

Etapa C

Una mezcla de éster de 3 [6-etil 1 ((R) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 ilo de ácido trifluoro metanosulfónico (200 mg) y NMP (6 ml) se agrega 1 ml $MeNH_2$ (4M en NMP) y la mezcla se calienta a 80 C durante 20 h La mezcla se vierte en agua (20 ml) se extrae con EtOAc (3x15 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro se obtiene después de purificación TLC preparativa (Hexano/EtOAc=2/1) LC MS m/z 381 45 (M+H)

Etapa D

{3-[6 Etil 1 ((R) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 il) metil amina (60 mg) en $CHCl_3$ (5 ml) se agrega N clorosuccinimida (23 mg) y la mezcla se calienta a 60 C durante 5 h Después la

reacción se completa el solvente se remueve y el producto crudo se purifica por TLC preparativo (Hexano/EtOAc=4/1) para dar 5-cloro-3 [6-etil 1 ((R) 2 metoxi 1 metil-etil) 3 metil-1H pirrolo[3 2 b]piridin 5 il]-6 isopropil-piridin 2 il}metil amino MS m/z 415 4 (M+H)

Etapa E

Una mezcla de {3-[6 Etil-1 ((R) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b] piridin 5 il]-6 isopropil piridin 2 il}-metil amina (130 mg) en CH_3CN (5 ml) se enfría a 0 C seguido por adición de NBS (61 mg) La mezcla resultante se agita a 0 C durante 30 min y luego esta se diluye con H_2O (20 ml) se extrae con EtOAc (3x25 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan La cromatografía de columna flash (Hexano/EtOAc=8/1) da el producto crudo {5 bromo-3 [6-etil-1 ((R) 2 metoxi-1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il]-6-isopropil piridin 2 il}-metil amina LC MS m/z 461 35 (M+H)

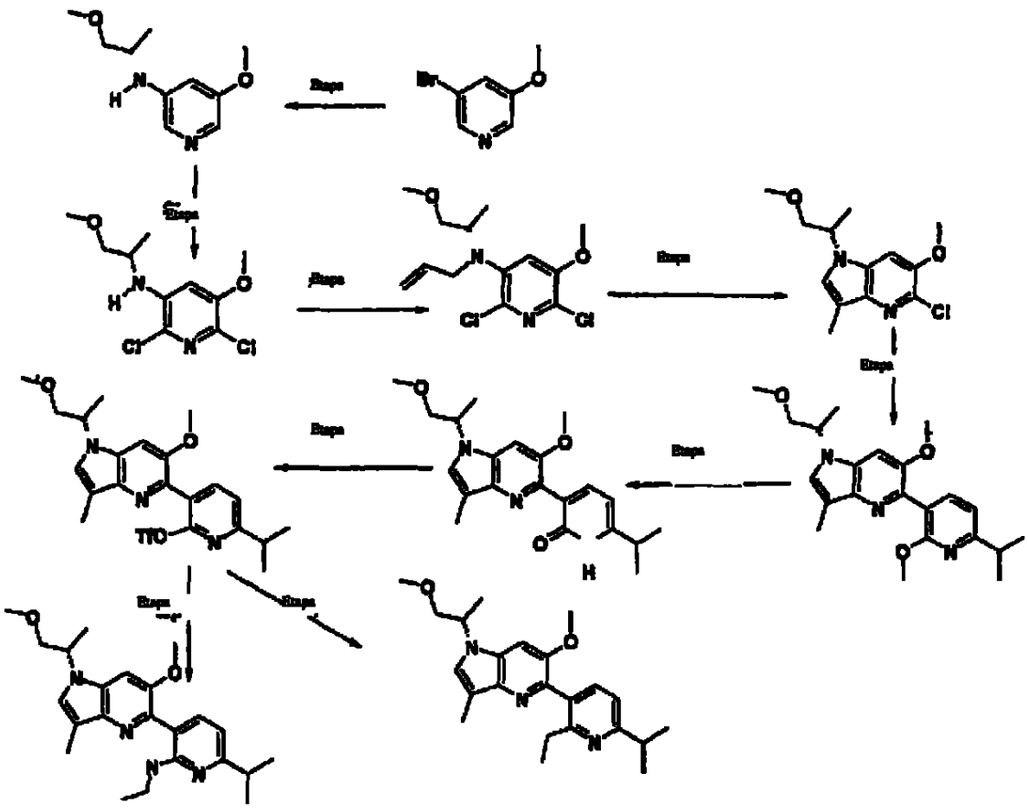
Etapa F

Una mezcla de {5-bromo-3 [6-etil 1 ((R)-2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 il}-metil amina (60 mg) K_2CO_3 2M (1 ml) ácido ciclopropil borónico (56 mg) en tolueno (5 ml) se desgasifica con N_2 durante 2 min seguido por adición de $Pd(PPh_3)_4$ (15 mg) La mezcla resultante se agita a 110 C durante 16 h antes esta se vierte en agua y se extrae con EtOAc (3xl5 ml) Las capas orgánicas combinadas se lavan con solución salina se secan sobre Na_2SO_4 y se evaporan El producto puro {5-ciclopropil 3 [6-etil 1 ((R) 2 metoxi 1 metil-etil)-3 metil 1H-pirrolo[3 2 b]piridin 5 il]-6 isopropil-piridin 2 il}metil-

amina se obtiene después de purificación TLC preparativa (CH_2Cl_2/MeOH=20/1) MS m/z 421 5 (M+H)

EJEMPLO 34

Síntesis de etil-[6 isopropil-3-[6-metoxi 1-((S) 2-metoxi 1 metil-etil)-3-metil 1H-pirrolo[3 2 b]piridin-5 il]-piridin 2-il}amina y 5 (2-etil-6 isopropil piridin-3 il)-6-metoxi 1-((S) 2 metoxi 1-metil-etil)-3-metil 1H-pirrolo[3 2 b]piridino



Etapa A

Análogo a la preparación de (5 bromo-piridin 3 il) [(S) 1 (terc-butil-dimetil silaniloximetil)-propil] amina la aminación mediada por paladio de 3-bromo 5-metoxipiridino (4 76g) con (S) 1 metoxi-2 propilamina (4 4 ml) da después de

purificación sobre gel de sílice ((S) 2 metoxi 1 metil-etil)-(5-metoxi piridin 3-il) amina LCMS m/z 197 1 (M+H) Rt 2 47 mins

Etapa B

La clorinación de ((S) 2 metoxi 1 metil-etil) (5-metoxi piridin 3 il) amina (5 30g) con N-clorosuccinimida (7 21g) da después de purificación sobre gel de sílice (2 6-dicloro-5 metoxi pirídin-3-il) ((S) 2 metoxi 1-metil-etil) amino LCMS m/z 265 2/267 1/269 1 (M+H) Rt 3 03 mins

Etapa C

Análogo a la síntesis de alil [(S) 1 (terc-butil-dimetil-silaniloximetil) propil] (2 5 6-tribromo-piridin 3 il)-amina la acilación de (2 6-dicloro-5-metoxi piridin 3 il) ((S) 2 metoxi 1-metil-etil) amina (5 38g) con yoduro de alilo (4 0 ml) produce después de purificación sobre gel de sílice alil-(2 6-dicloro-5-metoxi piridin 3 il) ((S) 2 metoxi 1 metil-etil)-amino LCMS m/z 305 1/307 1/309 0 (M+H) Rt 3 49 mins

Etapa D

Análogo a la síntesis de 5 6-dibromo-1 [(S) 1 (terc-butil-dimetil-silaniloximetil) propil]-3 metil 1H pirrolo[3 2 b]piridino la cristalización mediada por paladio de alil-(2 6-dicloro 5-metoxi piridin 3 il)-((S) 2 metoxi 1 metil-etil)-amina (5 13 g) produce después de purificación sobre gel de sílice 5-cloro-6 metoxi 1 ((S) 2 metoxi 1 metil-etil) 3 metil-1H pirrolo[3 2 b]piridino LCMS m/z 269 1/271 1 (M+H) Rt 2 41 mins

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Etapa E

Análogo a la síntesis de 6 bromo-1 [(S) 1 (terc-butil-dimetil-silaniloximetil) propil] 5-(6 isopropil 2 metoxi pirídin 3-il) 3 metil 1H pirrolo[3 2 b]piridino el acoplamiento mediado por paladio de 5-cloro-6 metoxi 1 ((S) 2-metoxi-1 metil-etil) 3-metil 1H pirrolo[3 2 b]pirídino (1 9g) con ácido 6-isopropil 2 metoxi 3 piridinoborónico (1 79g) produce después de purificación sobre gel de sílice 5-(6-isopropil 2 metoxi pirídin 3-il)-6 metoxi 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]pirídino LCMS m/z 384 2 (M+H) Rt 2 40 mins

Etapa F

Una solución de 5 (6 isopropil 2 metoxi pirídin 3 il)-6 metoxi 1 ((S) 2-metoxi 1 metil-etil)-3 metil 1H pirrolo[3 2 b]pirídino (890 mg) en ácido clorhídrico concentrado (60 mL 37%) se calienta a 55 C durante 16 horas La solución resultante se neutraliza con bicarbonato de sodio y se diluye con un poco de agua La mezcla se extrae con diclorometano (4x50 ml) y se secan sobre sulfato de magnesio La evaporación del solvente seguido por titulación con dietil éter da 6 isopropil 3-[6-metoxi 1 ((S) 2-metoxi 1-metil-etil) 3 metil 1H pirrolo[3 2 b]pirídin-5 il] pirídin 2-ol LCMS m/z 370 2 (M+H) Rt 2 01 mins

Etapa G

Análogo a la síntesis de éster de 3-(3 6-dimetil 1 propil 1H pirrolo[3 2 b]pirídin 5 il)-6 isopropil pirídin 2 ilo de ácido trifluoro-metanosulfónico la reacción de 6-isopropil 3 [6 metoxi 1-((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]pirídin 5 il] pirídin 2 ol (200 mg) con anhídrido tríflico (0 11 mL) en la presencia de trietil

amina (0 136 ml) da después de purificación sobre gel de sílice éster de 6 isopropil 3-[6 metoxi 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin-5-il]-piridin 2 ilo de ácido trifluoro-metanosulfónico LCMS m/z 502 1 (M+H) Rt = 3 29 mins

Etapa H

Análogo a la preparación de [3-(3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridin 5 il)-6 isopropil piridin 2 il]-etil-amina la reacción de éster de 6 isopropil 3 [6 metoxi 1 ((S)-2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 ilo de ácido trifluoro-metanosulfónico (70 mg) con solución de etil amina en THF (0 7mL 2M) produce después de purificación sobre gel de sílice da etil-[6 isopropil-3 [6 metoxi 1 ((S) 2 metoxi-1-metil-etil)-3-metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-amina LCMS m/z 397 3 (M+H) Rt= 2 14 mins

Etapa I

Análogo a la preparación de 5 (2-etil-6 isopropil piridin 3 il) 3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridino la reacción de éster de 6 isopropil 3 [6-metoxi-1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 ilo de ácido trifluoro-metanosulfónico (180 mg) con solución de trietilborano en hexanos (1 44mL 1 0M) produce después de purificación sobre gel de sílice 5 (2-etil-6-isopropil piridin 3 il)-6 metoxi 1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridino LCMS m/z 382 3 (M+H) Rt = 1 94 mins

Reemplazar la amina utilizada en la etapa H de Ejemplo 34 con varios otros reactivos amina se sintetizan los siguientes compuestos

{6 isopropil 3-[6 metoxi 1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-dimetil-amina Rt 1 97min m/z 397 2 (M+H)

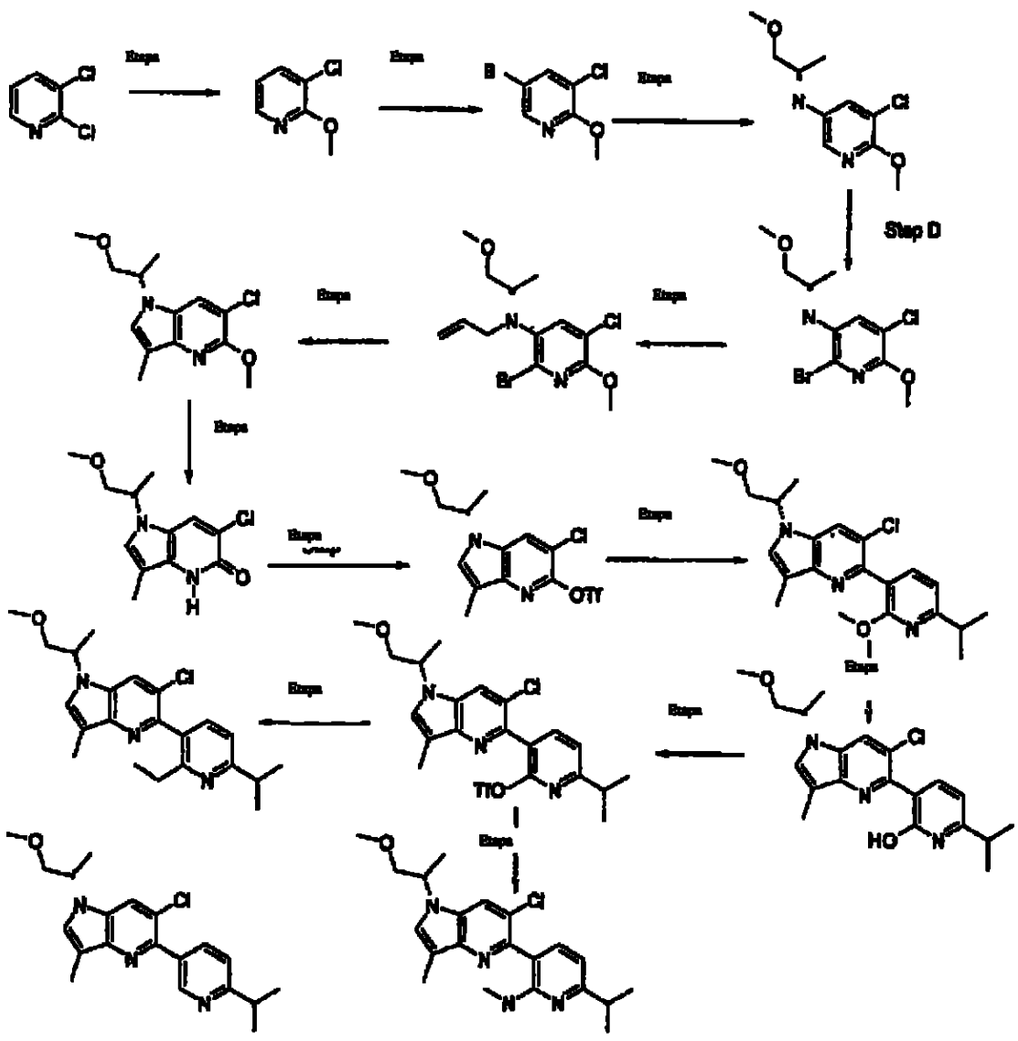
{6 isopropil 3 [6 metoxi 1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-metil amina Rt 1 93min m/z 383 3 (M+H)

EJEMPLO 35

Síntesis de 6-cloro-5-(2-etil-6-isopropil piridin-3 il) 1-((S) 2 metoxi 1-metil etil)-3-metil 1H-pirrolo[3 2 b]piridina 6-Cloro-5-(6 isopropil piridin-3-il) 1-((S) 2-metoxi 1-metil-etil)-3-metil 1H pirrolo[3 2-b]piridina y {3 [6-cloro 1-((S) 2 metoxi 1-metil-etil)-3-metil 1H pirrolo[3 2 b]piridin-5-il]-6-isopropil piridin 2 il}-metil-amina

Etapa

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Etapa A

Similar al procedimiento por Testaferre et al (Tetrahedron 41 No7 1373-1384 1985) una suspensión de 2 3-dicloropiridino (10g) en solución de metóxido de sodio en metanol (62mL 25%) se calienta a 55 C durante 15 horas La suspensión se filtra y el filtrado se evapora bajo volumen La mezcla se diluye con solución salina saturada se extrae con dietil éter (3x50 ml) y se secan sobre sulfato de magnesio Evaporación da directamente 3 cloro-2 metoxi piridino LCMS m/z 144 0/146 0 (M+H) Rt 2 29 mins

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Etapa B

Similar al procedimiento de Bargar et al (J Het Chem 22 1583 1985) una solución agitada de 3-cloro-2 metoxi-pirdino (9 3g) y acetato de sodio (5 4g) en ácido glacial acético (30 ml) se trata con bromo (6 7 ml) en forma de gotas durante 15 mins Después que la exotermia se ha depositado la mezcla se calienta a 80 C durante una hora La mezcla de reacción se enfría a temperatura ambiente y se diluye con éter (200 ml) y se lava con hidróxido de solución de sodio (1M) y solución de tiosulfato de sodio (100mL 2M) La capa de éter se seca sobre sulfato de magnesio y se evapora para dar 5-bromo 3 cloro-2-metoxi pirdino Este compuesto se utiliza sin purificación adicional en la siguiente reacción

Etapa C

Análogo a la preparación de ((S) 2 metoxi 1 metil-etil) (5 metoxi piridin 3 il) amina la aminación mediada por paladio de 5 bromo-3-cloro-2 metoxi piridino (4 0g) con (S) 1 metoxi 2 propilamina (2 1 mL) produce después de purificación sobre gel de sílice (5-cloro-6 metoxi piridin 3-il) ((S) 2-metoxi 1 metil-etil)-amina LCMS m/z 231 1/233 1 (M+H) Rt 2 19 mins

Etapa D

Análogo a la síntesis de (R) 2 (terc-butil-dimetil-silaniloxi) 1 metil-etil] (2 6 dibromo-5-etil piridin 3-il) amina la bromination de (5-cloro-6-metoxi pindin 3 il) ((S) 2-metoxi-1-metil-etil)-amina (1 350g) con N bromosuccinimida (782 mg) da después de purificación sobre gel de sílice (2 bromo 5 cloro-6 metoxi piridin 3 il)

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((S) 2 metoxı 1-metıl-etıl) amıno LCMS m/z 309 0/311 0/312 0 (M+H) Rt 3 00 mıns

Etapa E

Análogo a la síntesis de alıl-[(S) 1 (terc-butıl-dımetıl sılanıloxımetıl) propıl] (2 5 6 tnbromo pırıdın 3 ıl)-amına la alılación de (2 bromo-5-cloro-6 metoxı pırıdın-3 ıl) ((S) 2-metoxı 1 metıl-etıl)-amına (1 05g) con yoduro de alılo (0 68 mL) da después de purıficación sobre gel de sílice alıl (2 bromo-5-cloro-6 metoxı pırıdın 3 ıl)-((S) 2 metoxı 1-metıl-etıl) amına LCMS m/z 349 0/351 0/353 0 (M+H) Rt 3 32 mıns

Etapa F

Análogo a la síntesis de 5-cloro-6-metoxı 1 ((S) 2 metoxı-1 metıl-etıl) 3 metıl-1H pırrolo[3 2 b]pırıdıno la cıclızación medıada por paladıo de alıl (2 bromo-5-cloro-6 metoxı pırıdın 3-ıl) ((S) 2 metoxı 1 metıl-etıl)-amına (1 12g) produce después de purıficación sobre gel de sílice 6-cloro-5-metoxı 1 ((S) 2 metoxı 1 metıl-etıl) 3 metıl-1H pırrolo[3 2-b]pırıdıno LCMS m/z 269 1/271 1 (M+H) Rt 2 92 mıns

Etapa G

6-Cloro-5 metoxı 1 ((S) 2 metoxı 1 metıl-etıl)-3 metıl 1H pırrolo[3 2 b]pırıdıno (153 mg) se hace reaccionar con tıometóxıdo de sodıo (800 mg) La evaporación de los extractos de solvente y trituración del resıduo crudo con dıetıl éter da 6-cloro-1 ((S) 2 metoxı-1 metıl etıl) 3 metıl 1 4-dıhıdro-pırrolo[3 2 b]pırıdın 5-ona LCMS m/z 255 1/257 1 (M+H) Rt 2 03 mıns

Etapa H

Análogo a la síntesis de éster de 6-isopropil 3 [6 metoxi 1 ((S) 2 metoxi 1-metil etil) 3-metil 1H pirrolo[3 2 b]piridin 5-il] piridin 2 ilo de ácido trifluoro-metanosulfónico reacción de 6-cloro-1 ((S) 2 metoxi 1 metil-etil) 3 metil 1 4-dihidro-pirrolo[3 2 b]piridin 5-ona (340 mg) con anhídrido tríflico (0 27 ml) en la presencia de trietilamina (0 34 ml) produce después de purificación sobre gel de sílice éster de 6-cloro-1 ((S) 2 metoxi 1 metil-etil)-3 metil 1H pirrolo[3 2 b]piridin-5 ilo de ácido trifluoro-metanosulfónico LCMS m/z 387 0/389 0 (M+H) Rt = 3 22 mins

Etapa I

Análogos de la síntesis de 5 (6-isopropil 2-metoxi-piridin 3 il)-6-metoxi 1 ((S) 2 metoxi 1-metil-etil) 3 metil 1H pirrolo[3 2 b]piridino el acoplamiento mediado por paladio de éster de 6-cloro-1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin-5-ilo de ácido trifluoro-metanosulfónico (500 mg) con ácido 6 isopropil 2 metoxi 3-piridinoborónico (430 mg) produce después de purificación sobre gel de sílice 6-cloro-5-(6-isopropil 2 metoxi piridin 3 il) 1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridino LCMS m/z 388 2/390 2 (M+H) Rt 3 15 mins

Etapa J

Análogo a la preparación de 6-cloro 1 ((S) 2 metoxi 1 metil-etil) 3 metil 1 4 dihidro-pirrolo[3 2 b]piridin 5-ona 6-cloro-5-(6 isopropil 2 metoxi piridin 3 il)-1 ((S) 2 metoxi-1 metil-etil) 3 metil 1H pirrolo[3 2-b]piridino (300 mg) se hace reaccionar

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con tiometóxido de sodio (500 mg) La evaporación de los extractos de solvente y trituración del residuo crudo con dietil éter da 3 [6-cloro-1 ((S) 2 metoxi-1 metil etil) 3 metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil 1H piridin 2-ona LCMS m/z 374 2/376 2 (M+H) Rt 2 23 mins

Etapa K

Análogo a la preparación de éster 6 isopropil 3 [6 metoxi 1 ((S) 2 metoxi-1 metil etil) 3-methfl 1H pirrolo[3 2 b]piridin 5-il]-piridin 2 ilo de ácido trifluoro metanosulfónico la reacción de 3-[6-cloro 1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil 1H piridin 2-ona (250 mg) con anhídrido tríflico (0 14 ml) en la presencia de trietilamina (0 17 ml) da después de purificación sobre gel de sílice de éster de 3-[6-cloro-1 ((S) 2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 ilo de ácido trifluorometanosulfónico LCMS m/z 506 1/508 1 (M+H) Rt = 4 02 mins

Etapa L

Análogo a la preparación de 5 (2-etil-6 isopropil piridin 3 il)-6 metoxi 1 ((S) 2 metoxi 1-metil-etil)-3-metil 1H pirrolo[3 2-b]pirídino la reacción de éster de 3 [6-cloro 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 ilo de ácido trifluorometanosulfónico (145 mg) con solución de trietilborano en hexanos (1 2 mL 1 0 M) produce después de purificación sobre gel de sílice 6-cloro 5-(2-etil-6-isopropil-piridin 3 il) 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b] pirídino LCMS m/z 386 2/388 2 (M+H) Rt = 2 02 mins Aislado como un subproducto de esta reacción es 6-cloro 5 (6 isopropil-piridin 3

il) 1-((S) 2 metoxi-1 metil-etil) 3 metil 1H pirrolo[3 2-b]piridino LCMS m/z 358 2/360 2 (M+H) Rt = 2 15 mins

Etapa M

Análogo a la preparación de etil-{6 isopropil 3-[6-metoxi 1 ((S) 2 metoxi 1 metil etil)-3 metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-amina la reacción de éster de 3 [6-cloro-1 ((S) 2 metoxi-1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il]-6-isopropil piridin 2 ilo de ácido trifluoro-metanosulfónico (85 mg) con solución de metil amina en THF (0 9mL 2M) da después de purificación sobre gel de sílice {3 [6-cloro-1-((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 il}-metil amina LCMS m/z 387 2/389 2 (M+H) Rt = 2 09 mins

Reemplazando la amina en la etapa M del Ejemplo 35 con varios otros reactivos amina se sintetizan los siguientes compuestos

{3 [6 Cloro-1 (2 metoxi 1-metil-etil)-3 metil 1H pirrolo[3 2 b]piridin 5 il]-6-isopropil piridin 2 il}-dimetil-amina Rt 2 12min m/z 401 2 (M+H)

{3 [6 Cloro-1 (2 metoxi 1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5-il]-6-isopropil piridin 2 il}-etil-amina Rt 2 22min m/z 401 2 (M+H)

EJEMPLO 36

Síntesis de {3-[6-cloro 1-((R) 1 fluorometil 2-metoxi-etil)-3-metil 1H pirrolo[3 2 b]piridin-5 il]-6 isopropil piridin 2 il}-metil-amina y 6-cloro-5-(2

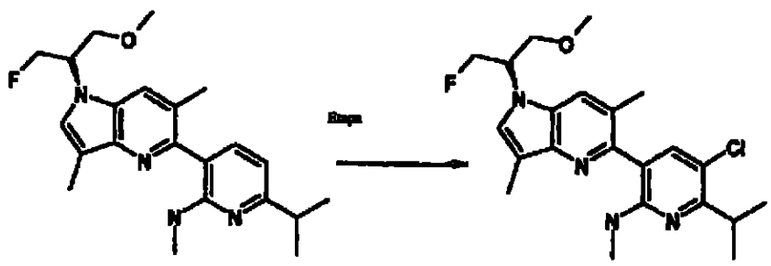
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etil-6 isopropil piridin-3-il) 1-((R) 1 fluorometil 2 metoxi-etil)-3-metil 1H pirrolo[3 2 b]piridino

Sustituyendo (R) 1 (terc-Butil-dimetil-silaniloximetil)-2 metoxi-etilamina por (S) 1 metoxi 2 propilamina en el esquema del Ejemplo 35 e introducir el grupo fluoro después de la etapa F como se describe en las etapas F y G del Ejemplo 13 da {3-[6-cloro-1 ((R) 1 fluorometil 2 metoxi-etil) 3 metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 il}-metil amina Rt 2 09min m/z 405 2 (M+H) y 6 cloro-5 (2 etil-6-isopropil piridin 3 il) 1 ((R) 1 fluorometil 2 metoxi-etil) 3 metil 1H pirrolo[3 2 b]piridino Rt 2 34min m/z 448 12 (M+H)

EJEMPLO 37

Síntesis de {5-Cloro-3 [1-((R) 1 fluorometil 2-metoxi-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridin-5-il]-6-isopropil-piridin 2-il}-metil-amina



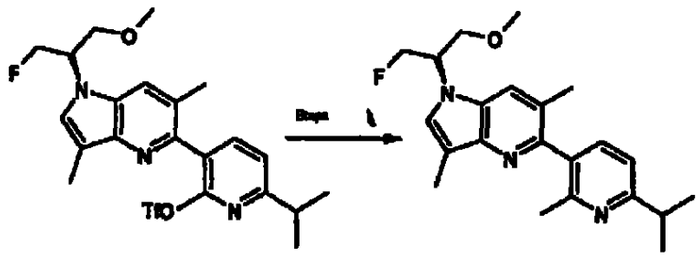
Etapa A

Se agrega N Clorosuccinimida (33 mg) a una solución de {3 [1 (1 fluorometil 2 metoxi-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 il}-metil amina (94 mg) en cloroformo (3 mL) Después de 18 hr addicionales se agrega N clorosuccinimida (10 mg) y luego después de 5 min adicionales se agrega agua

(10 ml) y diclorometano (10 ml) a la mezcla de reacción La capa orgánica se separa se seca y se evapora para dar después de cromatografía sobre gel de sílice {5-Cloro-3 [1 ((R) 1 fluorometil 2 metoxi-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-6-isopropil-piridin 2 il}-metil-amina Rt 2 67min m/z 419 2 (M+H)

EJEMPLO 38

Síntesis de 1-((R) 1 fluorometil 2-metoxi-etil)-5-(6-isopropil 2-metil piridin-3 il)-3 6-dimetil 1H-pirrolo[3 2 b]piridino



Etapa A

Éster de 3-[1 (1 fluorometil-2 metoxi-etil) 3 6-dimetil 1H pirrolo[3 2-b]piridin-5 il]-6-isopropil piridin 2 ilo de ácido Trifluoro-metanosulfónico (97 mg) cloruro de bis (trifenilfosfina) paladio (II) (4 mg) y cloruro de litio (25 mg) se introducen en un tubo de vidrio que se llena luego con nitrógeno Se agregan DMF (2 ml) y tetrametilestaño (30uL) el tubo se cierra con una tapa y la mezcla de reacción se calienta a 100 C durante la noche Se agrega agua (2 ml) y EtOAc (2 ml) y luego la capa orgánica se separa La capa orgánica se extrae tres veces más con EtOAc y luego la fase orgánica combinada se seca y evapora para dar después de purificación con gel de sílice 1 ((R) 1 Fluorometil 2 metoxi-etil) 5 (6 isopropil 2 metil piridin 3-il) 3 6-dimetil 1H pirrolo[3 2 b]pindino Rt 1 83min m/z 370 2 (M+H)

EJEMPLO 39

En una forma análoga a la síntesis de 1 ((R) 1 fluorometil 2 metoxi-etil) 5-(6 isopropil 2-metil piridin 3-il)-3 6-dimetil 1H-pirrolo[3 2 b]piridino éster de 3 [6-cloro-1 ((S) 2 metoxi 1-metil-etil) 3 metil 1H pirrolo[3 2-b]piridin 5 il]-6 isopropil piridin 2 ilo de ácido trifluormetanosulfónico produce 6-cloro-1 ((R) 1 fluoro-metil 2 metoxi-etil) 5-(6 isopropil 2 metil piridin 3 il) 3-metil 1H pirrolo[3 2 b]piridino Rt 2 17min m/z 390 11 (M+H)

EJEMPLO 40

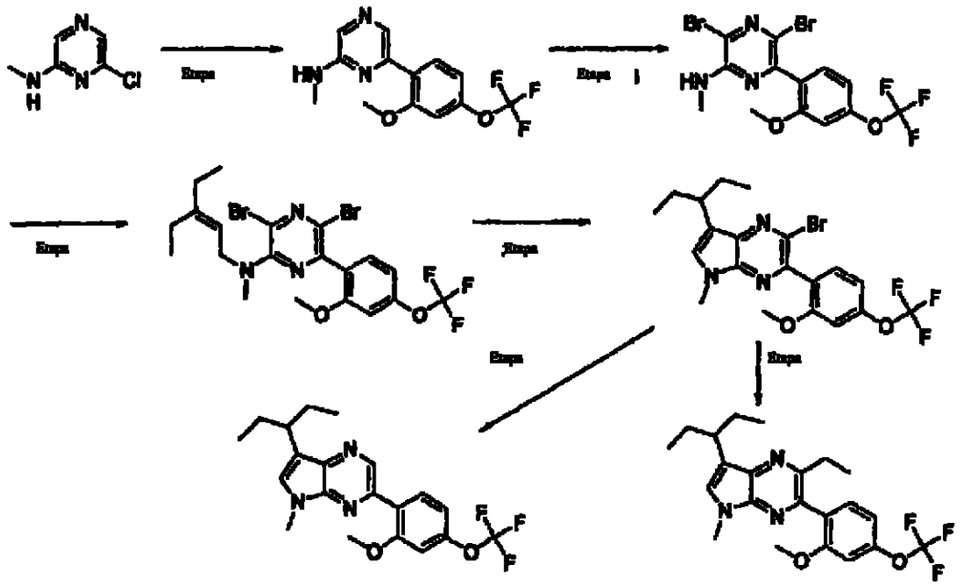
Síntesis de Etil-{3 [1-((R) 1 fluorometil 2-metoxi-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridin-5 il]-6-isopropil piridin 2 il}-amina

En una forma análoga a la síntesis de {3 [1 ((R) 1 Fluorometil 2 metoxi-etil) 3 6-dimetil 1H pirrolo[3 2-b]pindin 5 il]-6 isopropil-pindin 2 il}-metil-amina éster de 3 [1 (1 fluorometil 2 metoxi-etil) 3 6-dimetil 1H-pirrolo[3 2 b]pindin 5 il]-6 isopropil pindin 2 ilo de ácido trifluorometanosulfónico y etilamina produjo etil-{3 [1 ((R) 1 fluorometil 2 metoxi-etil) 3 6-dimetil 1H pirrolo[3 2 b]pindin 5 il]-6 isopropil piridin 2 il}-amina Rt 2 03min m/z 399 2 (M+H)

EJEMPLO 41

Síntesis de 2 bromo 7-(1-etil propil)-3-(2-metoxi-4-trifluorometoxi fenil)-5 metil-5H-pirrolo[2 3 b]pirazina 7-(1-etil propil)-3-(2-metoxi-4-trifluorometoxi

fenil)-5-metil-5H-pirrolo[2 3-b]pirazina y 2-etil 7-(1-etil-propil)-3-(2-metoxi-4-trifluorometoxi fenil)-5 metil-5H-pirrolo[2 3 b]pirazina



Etapa A

Una mezcla de (6-cloro-pirazin 2 il) metil-amina (431 mg 3 mmol) ácido 2 metoxi 4-trifluorometoxifenil borónico (780 mg 3 3 mmol) en Na_2CO_3 2M (3 mL 6 mmol) y tolueno (3 mL) se trata con $Pd(PPh_3)_4$ (50 mg) bajo nitrógeno a 80 C durante 16 h Después de enfriar a temperatura ambiente el producto se extrae con acetato de etilo (3 x 10 mL) secado concentrado y purificado por cromatografía de columna de gel de sílice para dar [6 (2 metoxi-4-trifluorometoxi-fenil) pirazin 2 il] metil-amina LC MS (M + 1) 300

Etapa B

A una solución de [6-(2 metoxi-4 trifluorometoxi fenil)-pirazin 2 il] metil-amina (1 2 g 4 mmol) en cloroformo (20 mL) se agrega NBS (1 78 g 10 mmol) en una

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porción a 0 C La mezcla se agita luego a temperatura ambiente durante 15 min seguido por concentración y purificación por cromatografía de columna de gel de sílice para proporcionar [3 5-dibromo-6 (2 metoxi-4 trifluorometoxi fenil) pirazin 2 il] metil-amina LC MS (M + 1) 458

Etapa C

A una solución de NaH (95% 65 mg 4 5 mmol) y se agrega Bu_4NBr (144 mg 0 45 mmol) en NMP anhidro (2 mL) en forma de gotas a una solución de [3 5-dibromo-6 (2 metoxi-4 trifluorometoxi fenil) pirazin 2 il]-metil amina (1 37 g 3 mmol) en NMP (10 mL) bajo nitrógeno a temperatura ambiente en 5 min La mezcla se continua agitando a temperatura ambiente durante 1 h seguido por adición de 1 cloro-3-etil pent 2-eno (594 mg 4 5 mmol) La mezcla se calienta luego a 65 C durante 16 h Después de enfriar a temperatura ambiente el producto se extrae con acetato de etilo (3 x 20 mL) lavado con agua (2 x 8 mL) y solución salina (10 mL) se seca se concentra se y purifica por cromatografía de columna de gel de sílice para dar [3 5-dibromo-6 (2 metoxi-4 trifluorometoxi fenil) pirazin 2 il] (3-etil pent 2-enil) metil-amina

Etapa D

Una mezcla de [3 5-dibromo-6-(2 metoxi-4-trifluorometoxi fenil) pirazin 2 il] (3-etil pent 2-enil) metil-amina (1 77 g 3 2 mmol) Bu_4NBr (1 02 g 3 2 mmol) K_2CO_3 (1 33 g 9 6 mmol) y $Pd(OAc)_2$ en DMF anhidro (20 mL) bajo nitrógeno se calienta a 90 C durante 1 h Después de enfriar a temperatura ambiente la reacción se apaga por adición de agua (10 mL) El producto se extrae con acetato de etilo (3 x 20 mL) se lava con agua (2 x 8 mL) y solución salina (10 mL) se seca se

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concentra y purifica por cromatografía de columna de gel de sílice para dar 2 bromo-7 (1-etil-propil) 3 (2 metoxi-4 trifluorometoxi fenil) 5 metil 5H pirrolo[2 3 b]pirazina LC MS (M + 1) 472

Etapa E

Una solución de 2 bromo 7 (1-etil-propil)-3 (2 metoxi-4 trifluorometoxi fenil)-5 metil 5H pirrolo[2 3 b]pirazina (50 mg 0 106 mmol) en acetato de etilo (5 mL) se hidrogena con 5% de Pd C (10 mg) bajo atmósfera a temperatura ambiente durante la noche Después de filtración y concentración el producto se purifica por cromatografía de columna de gel de sílice para dar 7 (1-etil propil)-3 (2 metoxi-4-trifluorometoxi fenil)-5 metil 5H pirrolo[2 3 b]pirazina ^{1}H RMN ($CDCl_3$ δ) 0 85 (t J= 7 2 Hz 6H) 1 82 (m 4H) 2 87 (m 1H) 3 87 (s 1H) 3 88 (s 3H) 6 86 (s 1H) 6 98 (d J= 8 4 Hz) 7 19 (s 1H) 7 87 (d J= 8 4 Hz 1H) 8 90 (s 1H) LC MS (M + 1) 394

Etapa F

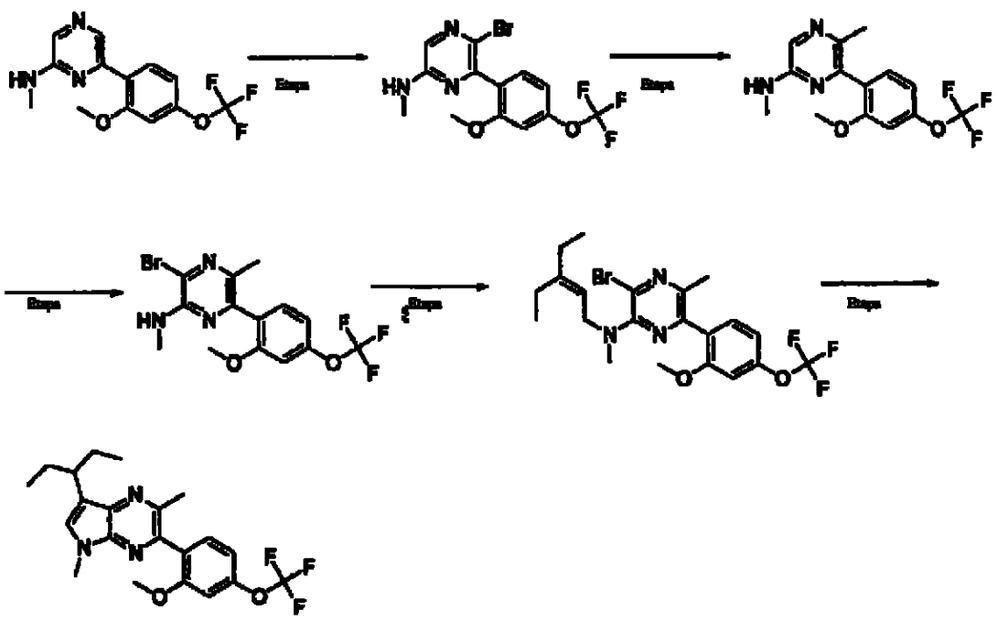
Una mezcla de 2 bromo-7 (1-etil propil) 3 (2-metoxi-4-trifluorometoxi fenil) 5-metil 5H pirrolo[2 3 b]pirazina (47 mg 0 1 mmol) Et_3B (solución en hexano 1M 0 2 mL 0 2 mmol) en Na_2CO_3 2M (0 5 mL 1 mmol) y tolueno (1 mL) se trata con $Pd(PPh_3)_4$ (10 mg) bajo nitrógeno a 90 C durante 16 h Después de enfriar a temperatura ambiente el producto se extrae con acetato de etilo (3 x 10 mL) se seca se concentra y purifica por cromatografía de columna de gel de sílice para dar 2-etil 7 (1-etil propil) 3 (2 metoxi-4-trifluorometoxi fenil) 5 metil 5H pirrolo[2 3-b]pirazina ^{1}H RMN ($CDCl_3$ δ) 0 87 (t J=7 6Hz 6H) 1 17 (t J = 7 6 Hz 3H) 1 82

347

(m 4H) 2 69 (m 2H) 2 92 (m 1H) 3 77 (s 1H) 3 81 (s 3H) 6 83 (s 1H) 6 94 (d J= 8 0 Hz) 7 12 (s 1H) 7 31 (d J= 8 0 Hz 1H) LC MS (M + 1) 408

EJEMPLO 42

Síntesis de 2 metil 7-(1-etil propil)-3-(2 metoxi-4-trifluorometoxi fenil) 5-metil 5H-pirrolo[2 3 b]pirazina



Etapa A

A una solución de [6 (2 metoxi-4-trifluorometoxi fenil) pirazin 2 il] metil-amina (3 g 10 mmol) en cloroformo (25 mL) se agrega NBS (2 13 g 12 mmol) en una porción a 0 C La mezcla se agita luego a temperatura ambiente durante 30 min seguido por concentración y purificación por cromatografía de columna de gel de sílice para suministrar [5 bromo-6 (2 metoxi-4 trifluorometoxi fenil)-pirazin 2 il] metil amina LC MS (M + 1) 378

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Etapa B

Una mezcla de [5-bromo-6 (2 metoxi-4-trifluorometoxi fenil) pirazin 2 il] metil amina (120 mg 0 32 mmol) $MeB(OH)_2$ (192 mm 3 2 mmol) en Na_2CO_3 2M (2 mL 4 mmol) y tolueno (2 mL) se trata con $Pd(PPh_3)_4$ (20 mg) bajo nitrógeno a 85 C durante 16 h Después de enfriar a temperatura ambiente el producto extraido con acetato de etilo (3 x 10 mL) secado concentrado y purificado por cromatografía de columna de gel de sílice para dar [6 (2 metoxi-4-trifluorometoxi fenil) 5 metil-pirazin 2 il] metil-amina

Etapa C

[3-bromo-6 (2-metoxi-4 trifluorometoxi fenil) 5 metil-pirazin 2 il] metil amina se prepara por el mismo procedimiento como se describe en la **Etapa A** LC MS 392

Etapa D

[3-bromo-6 (2 metoxi-4 trifluorometoxi fenil) 5-metil pirazin 2 il] (3-etil pent 2-enil) metil amina se prepara por el mismo procedimiento para [3 5-dibromo-6 (2 metoxi 4 trifluorometoxi fenil) pirazin 2 il]-(3-etil pent 2-enil) metil-amina

Etapa E

7 (1 Etil propil) 3 (2 metoxi-4 trifluorometoxi fenil) 2 5-dimetil 5H pirrolo[2 3 b]pirazina se prepara por el mismo procedimiento para 2 bromo 7 (1-etil propil) 3 (2 metoxi-4-trifluorometoxi fenil) 5 metil 5H pirrolo[2 3 b]pirazina ^1H RMN ($CDCl_3$ δ) 0 86 (t J= 7 6 Hz 6H) 1 83 (m 4H) 2 42 (s 3H) 2 93 (m 1H) 3 78 (s 1H)

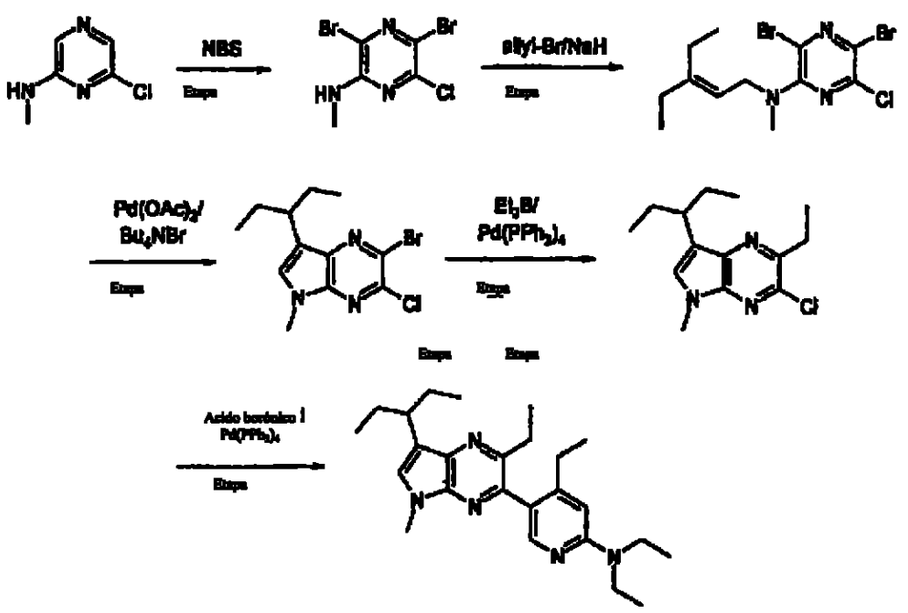
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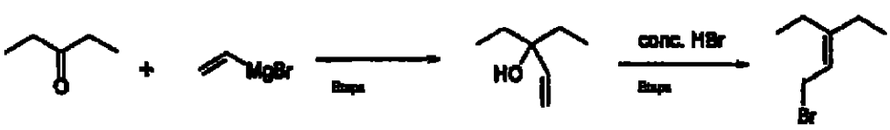
3 81 (s 3H) 6 83 (s 1H) 6 94 (d J= 8 0 Hz) 7 12 (s 1H) 7 31 (d J= 8 0 Hz 1H)

LC MS (M + 1) 422

EJEMPLO 43

Síntesis de N N-dietil-{4-etil-5 [2-etil 7-(1-etil propil)-5-metil-5H pirrolo[2 3 b]pirazin-3 il]-piridin 2 il}-amina





Etapa A

El previamente descrito 2-cloro-4 metilaminopirazina (40 0g) se disuelve en cloroformo (500 ml) y se agrega NBS (104 0g) Después de agitarse durante 16h la mezcla amarillenta se pone en agua (500 ml) y bicarbonato de sodio saturado

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(100 ml) se extrae con acetato de etilo/hexano (1/3 2x400 ml) y se seca sobre sulfato de magnesio El crudo se lava a chorro a través de un tapón de gel de sílice (acetato de etilo/hexano = 1/3) y se usa sin ninguna otra purificación TLC Rf= 0 63 (acetato de etilo/hex = 1/3)

Etapa B

El dibromuro crudo (73 69g) de la Etapa A y el ultimo descrito 3 3-dietilbromuro de alilo (84 40g etapa F+G) se disuelven en DMF (400 ml) Hidruro de sodio (15 50g) se agrega en porciones y la reacción se agita durante 30 min a TA La mezcla se coloca entonces en agua (2000 ml) y se extrae con acetato de etilo/hexano (1/6 4x700 ml) Las capas orgánicas combinadas se lavan con agua (200 ml) se secan sobre sulfato de magnesio y se filtran directamente a través de un tapón de gel de sílice (200g) El material crudo se usa directamente en la Etapa C TLC Rf = 0 90 (EtOAc/hex= 1/6)

Etapa C

El compuesto de alilo crudo (116 0g) de la Etapa B bromuro de tetrabutilamonio (75 3g) acetato de paladio (5 2g) y carbonato de potasio (97 0g) se disuelven en DMF (1200 ml) Después de calentarse a 80 C durante 6h la mezcla se trabaja de acuerdo con la Etapa B La purificación final sobre gel de sílice produce el compuesto bicíclico TLC Rf= 0 59 (EtOAc/hex = 1/6)

Etapa D

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El compuesto bicíclico (1 83g) de la Etapa C se disuelve en tolueno (50 ml) Después de desgasificar se agrega tetrakis (trifenilfosfina) paladio (0) (0 67g) Una segunda desgasificación es seguida por adicion de trietilborano (28 9mL en hexano) y de una solución de carbonato de potasio 2N (6 0 ml) luego la reacción se calienta a 80 C durante 36h La mezcla amarillenta se coloca entonces en agua (200 ml) se extrae con DCM (3x150 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el derivado de etilo LCMS m/z 266 14 (M+H)

Etapa E

El derivado de etilo (500 mg) de la Etapa D y el previamente descrito ácido 2 dietilamino-4-etil 5 piridino borónico (526 mg) se disuelven en DME (15 mL) Después de desgasificar se agrega tetrakis (trifenilfosfina) paladio (0) (183 mg) Una segunda desgasificación es seguida por adición de solución de carbonato de sodio1N (3 2 ml) luego la reacción se calienta a 80° C durante 40h La mezcla amarillenta se coloca entonces en agua (100 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 408 37 (M+H)

Etapa F

3 Pentanona (73 9 ml) en THF (300 ml) se agrega lentamente a bromuro de magnesio vinilo (800mL en THF 1N) a ta Después de agitarse durante 24h la mezcla se pone en agua (2500 mL) y bicarbonato de sodio saturado (500 ml) se extrae con DCM (lxl500mL 2x500 mL) y se seca sobre sulfato de magnesio La mezcla cruda se utiliza sin ninguna purificación adicional en la etapa G

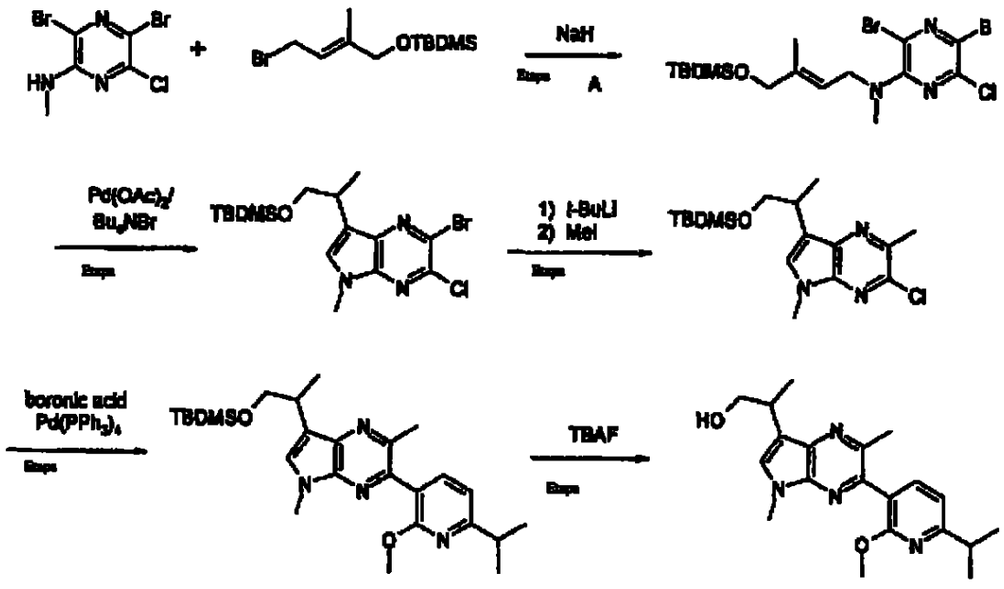
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Etapa G

La mezcla cruda (82 0 g) de la etapa F se disuelve en HBr conc (250 ml) Luego de 20 min o una vez que el control de RMN muestra la conversión completa la mezcla oscura se pone en agua (500 ml) se extrae con DCM (3x250 ml) y se seca sobre sulfato de magnesio La mezcla cruda se utiliza sin ninguna purificación adicional en la Etapa B

EJEMPLO 44

Síntesis de 2 [3-(6 isopropil 2-metoxi piridin-3-il) 2 5-dimetil-5H-pirrolo[2 3 b]pirazin 7 il]-propan 1-ol



Etapa A

El previamente descrito 2 6-dibromo-3-cloro-5-metilaminopirazina (550 mg) y el bromuro alílico mostrado (560mg sintetizado idénticamente al Me-regioisómero

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descrito por Enders *et al* Synlett 2002 2280) se disuelven en DMF (10 ml) Después de adición de hidruro de sodio (91 mg) la mezcla de reacción roja oscura se agita durante 15 min Posteriormente la mezcla se pone en agua (200 ml) y bicarbonato de sodio saturado (100 ml) se extrae con etil éter (2x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto alílico TLC Rf= 0 69 (EtOAc/hex = 1/6)

Etapa B

El compuesto alílico (892 mg) de la Etapa A bromuro de tetrabutilamonio (575 mg) acetato de paladio (40 mg) y carbonato de potasio (737 mg) se disuelven en DMF (10 ml) Después de calentar a 80 C durante 30 min la mezcla se trabaja de acuerdo con la Etapa A La purificación sobre gel de sílice produce el producto Heck LCMS m/z 417 93 (M+H)

Etapa C

El producto Heck (356 mg) de la Etapa B se disuelve en THF (2 5 ml) y se agrega una solución de t BuLi (1 05mL 1 7N en pentano) en THF (8 5 ml) a 78 C Después de agitarse durante 10 min yoduro de metilo (0 21 ml) se agrega y la mezcla de reacción se agita durante otra 1 h a 78 C Posteriormente la mezcla se pone en agua (100 ml) y bicarbonato de sodio saturado (50 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el derivado de metilo LCMS m/z 354 12 (M+H)

Etapa D

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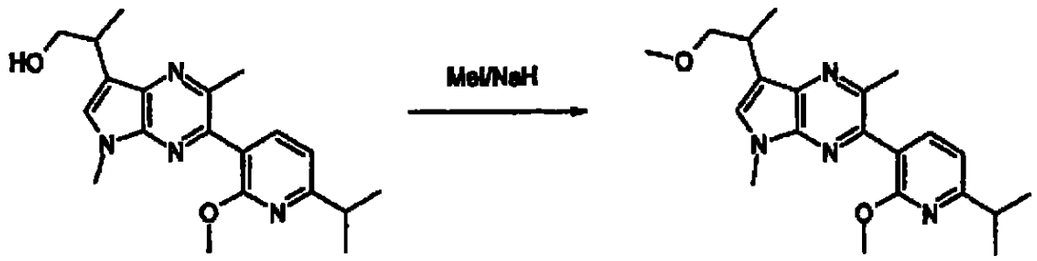
El proeducto de metilo de la Etapa C (238 mg) y el ácido 2 isopropil-6-metoxi-5 piridino borónico previamente descrito (158 mg) se disuelven en DME (5 0 ml) Después de desgasificar se agrega tetrakis (trifenilfosfina) paladio (0) (77 mg) Una segunda desgasificación es seguida por adición de una solución de carbonato de sodio (1 35 ml) en donde la reacción se calienta a 80 C durante 3h La mezcla amarillenta se coloca entonces en agua (100 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el producto acoplado LCMS *m/z* 469 15 (M+H)

Etapa E

El producto Suzuki de la Etapa D se disuelve en THF (5 0 ml) Después de adición de monohidrato de TBAF (650 mg) la mezcla de reacción se agita durante 30 min Posteriormente la solución amarilla se pone en agua (100 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 355 16 (M+H)

EJEMPLO 45

Síntesis de 3-(6 isopropil 2 metoxi-piridin-3 il) 7-(2 metoxi 1-metil-etil) 2 5 dimetil-5H pirrolo[2 3-b]pirazina

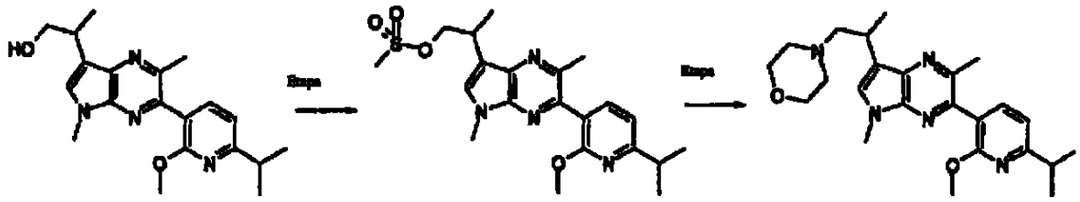


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2 [3 (6 isopropil 2 metoxi piridin 3-il) 2 5-dimetil 5H pirrolo[2 3 b]pirazin 7 il]-propan 1 ol (33 mg) se disuelve en THF (5 0 ml) Después de adición de hidruro de sodio (74 mg) la mezcla nubosa se agita durante 5 min antes se agrega yoduro de metilo (0 23 ml) La reacción se agita durante 16h se pone en agua (100 ml) y bicarbonato de sodio saturado (10 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 369 15 (M+H)

EJEMPLO 46

Síntesis de 3-(6 isopropil 2-metoxi-piridin-3 il) 2 5-dimetil 7-(1-metil 2 morfolin-4-il-etil)-5H pirrolo[2 3-b]pirazina



Etapa A

2 [3 (6 isopropil 2 metoxi piridin 3-il) 2 5-dimetil 5H pirrolo[2 3-b]pirazin 7 il] propan 1-ol (142 mg) se disuelve en DCM (5 0 ml) y se enfría a 0 C Se agregan cloruro de Mesilo (34gL) y trietilamina (78µL) antes la reacción se agita durante 30 min a 0 C Posteriormente la solución amarilla se pone en agua (100 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La mezcla cruda se lleva a la Etapa B sin ninguna purificación adicional LCMS m/z 433 07 (M+H)

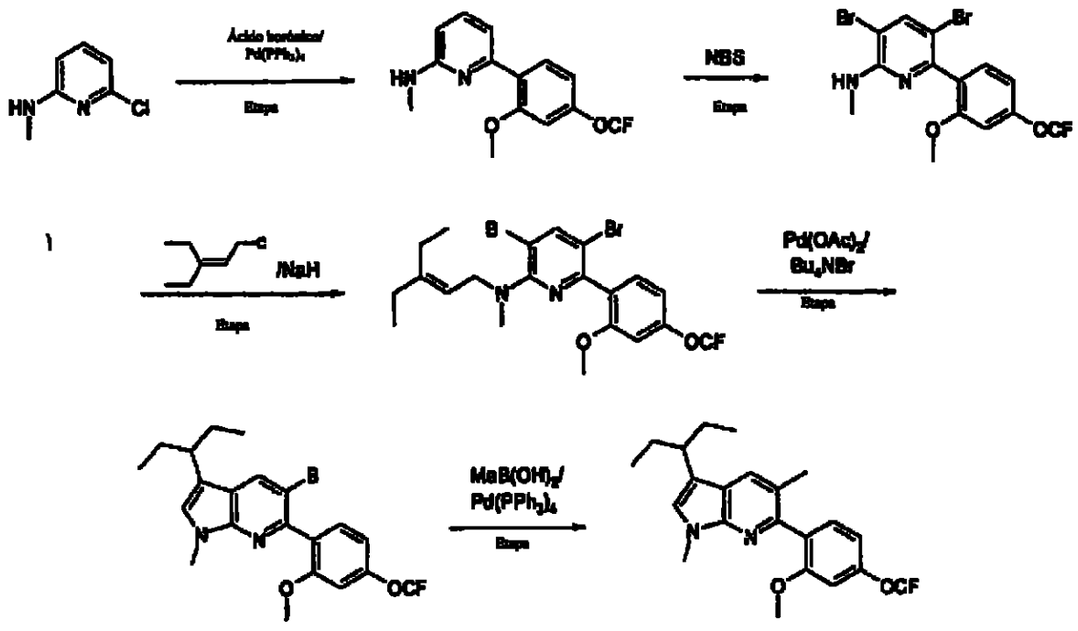
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Etapa B

El mesilato (54 mg) de la Etapa A se disuelve en acetonitrilo (1 0 ml) Después de adición de morfolino (200 mg) la reacción se calienta a 80 C durante 3h Posteriormente la solución clara se pone en agua (100 ml) se extrae con DCM (3x100 ml) y se seca sobre sulfato de magnesio La purificación sobre gel de sílice produce el compuesto del título LCMS m/z 424 13 (M+H)

EJEMPLO 47

Síntesis de 3-(1-etil-propil)-6-(2-metoxi-4-trifluorometoxi fenil) 1 5-dimetil 1H pirrolo[2 3 b]piridino



Etapa A

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El previamente descrito 2-cloro-6 metilaminopiridino (670 mg) El también previamente descrito ácido 2 metoxi-4-trifluorometoxifenil borónico (1 37g) y $Pd(PPh_3)_4$ (115 mg) se disuelven en tolueno (30 ml) Después de adición de Na_2CO_3 2N (6 ml) la mezcla se desgasifica y luego se calienta a 85 C durante la noche La solución se diluye con EtOAc y se lava con NaOH 2N H_2O solución salina y se seca sobre $MgSO_4$ La purificación sobre gel de sílice produjo el producto Suzuki ^1H RMN ($CDCl_3$ δ ppm) 7 78 (1H d J= 8 4 Hz) 7 49 (1H t J= 7 6 Hz) 7 08 (1H d J= 7 6 Hz) 6 90 (1H dd J= 7 4 2 0Hz) 6 80 (1H d J= 2 0Hz) 6 34 (1H J= 8 4Hz) 4 66 (1H brs) 3 84 (3H s) 2 94 (3H d J= 5 0Hz)

Etapa B

A una solución enfriada del producto Suzuki de la Etapa A (1 0g) en $CHCl_3$ se agrega una solución de NBS (1 22g) en $CHCl_2$ a 0 C durante 30 min Después de agitarse a TA durante 1hr la mezcla de reacción se evapora El residuo se purifica entonces sobre gel de sílice para producir el bromuro ^1H RMN ($CDCl_3$ δ ppm) 7 80 (1H s) 7 28 (1H d J= 8 4 Hz) 6 90 (1H dd J= 8 4 I IHz) 6 79 (1H s) 5 03 (1H brs) 3 82 (3H s) 2 98 (3H d J= 5 0Hz)

Etapa C

A una solución del bromuro crudo (1 1g) de la Etapa B en NMP (10 ml) se agrega NaH (60% 0 195g) Después de agitarse durante 2h cloruro de 3 3-dietilalilo desetiladas en forma fresca (0 414g preparadas en forma análoga al bromuro de 3 3-dietilalilo descrito) se agrega a la mezcla de reacción Agitación durante 1h adicional es seguida por apagado con H_2O y la extracción con EtOAc La capa orgánica se lava con H_2O solución salina y se seca sobre Na_2SO_4 La purificación

sobre gel de sílice produjo el compuesto alilo ^{1}H RMN ($CDCl_3$ δ ppm) 7 95 (1H s) 7 28 (1H d J= 8 3 Hz) 6 90 (1H d J=8 3Hz) 6 79 (1H s) 5 30 (1H m) 3 92 (2H d J= 6 6Hz) 3 81 (3H s) 2 87 (3H s) 2 06 (4H m) 1 01 (3H t J= 7 5Hz) 0 94 (3H t J= 7 5Hz)

Etapa D

El compuesto alilo de la Etapa C (330 mg) $Pd(OAc)_2$ (40 mg) bromuro de tetrabutilamonio (219 mg) y K_2CO_3 (250 mg) se disuelven en DMF (3 mL) desgasificado y calentado a 80 C durante la noche La mezcla se diluye con EtOAc y se lava con H_2O solución salina y se seca sobre $MgSO_4$ La purificación sobre gel de sílice produjo el producto Heck ^{1}H RMN ($CDCl_3$ δ ppm) 8 11 (1H s) 7 31 (1H d J= 8 3 Hz) 6 94 (2H m) 6 82 (1H d J= 1 7 Hz) 3 81 (3H s) 3 80 (3H s) 2 58 (1H m) 1 62 1 79 (4H m) 0 85 (6H t J= 7 3Hz)

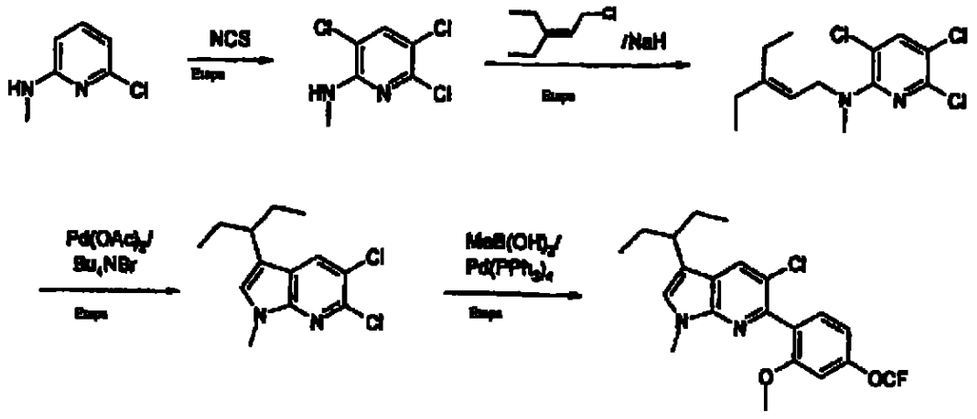
Etapa E

El producto Heck de la Etapa D (80 mg) ácido metilborónico (60 mg) y $Pd(PPh_3)_4$ (10 mg) se disuelven en tolueno (5 mL) Después de adición de Na_2CO_3 2N (3 mL) la mezcla de reacción se desgasifica y luego se calienta a 85 C durante la noche Posteriormente la solución se diluye con EtOAc y se lava con NaOH 2N H_2O y solución salina antes de ser secada sobre $MgSO_4$ La purificación sobre gel de sílice produjo el compuesto del título ^{1}H RMN ($CDCl_3$ δ ppm) 7 73 (1H s) 7 32 (1H d J = 8 2 Hz) 6 93 (1H d J = 8 2 Hz) 6 88 (1H s) 6 82 (1H s) 3 81 (3H s) 3 78 (3H s) 2 18 (3H s) 1 68-1 79 (4H m) 0 86 (6H t J= 7 3Hz)

EJEMPL 48

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Síntesis de 5-cloro-3-(1-etil propil)-6-(2-metoxi-4-trifluorometoxi fenil) 1-metil 1H-pirrolo[2 3 b]piridino



Etapa A

Se agrega NCS (2 95g) a una solución del 2-cloro-6 metilaminopindino previamente descrito (1 43g) en acetonitrilo (40 ml) luego la mezcla de reacción se calienta a 70 C durante 48h Posteriormente la solución amarilla se diluye con EtOAc se lava con H_2O solución salina y se seca sobre Na_2SO_4 La purificación sobre gel de sílice produjo el tricloruro ^1H RMN ($CDCl_3$ δ ppm) 7 50 (1H s) 5 07 (1H brs) 3 04 (3H d J= 5 0Hz)

Etapa B

A una solución del tricloruro de la Etapa A (1 03g) en NMP (20 ml) se agrega bromuro de tetrabutilamonio (0 2g) y NaH (60% 0 38g) Después de agitarse a TA durante 3h se agrega cloruro de 3 3-dietilalilo (0 97g preparado en forma análoga al descrito anteriormente bromuro de 3 3-dietilalilo) y la mezcla de reacción se agita durante 36h adicionales La solución amarilla luego se apaga con agua y se

extrae con EtOAc La capa orgánica se lava con agua solución salina y se seca sobre $MgSO_4$ para producir la alilamina cruda que se utiliza en la Etapa C sin ninguna purificación adicional ^1H RMN ($CDCl_3$ δ ppm) 7 58 (1H s) 5 23 (1H t J = 6 7Hz) 3 96 (2H d J = 6 7Hz) 2 92 (3H s) 2 05 2 09 (4H m) 0 94 1 00 (6H m)

Etapa C

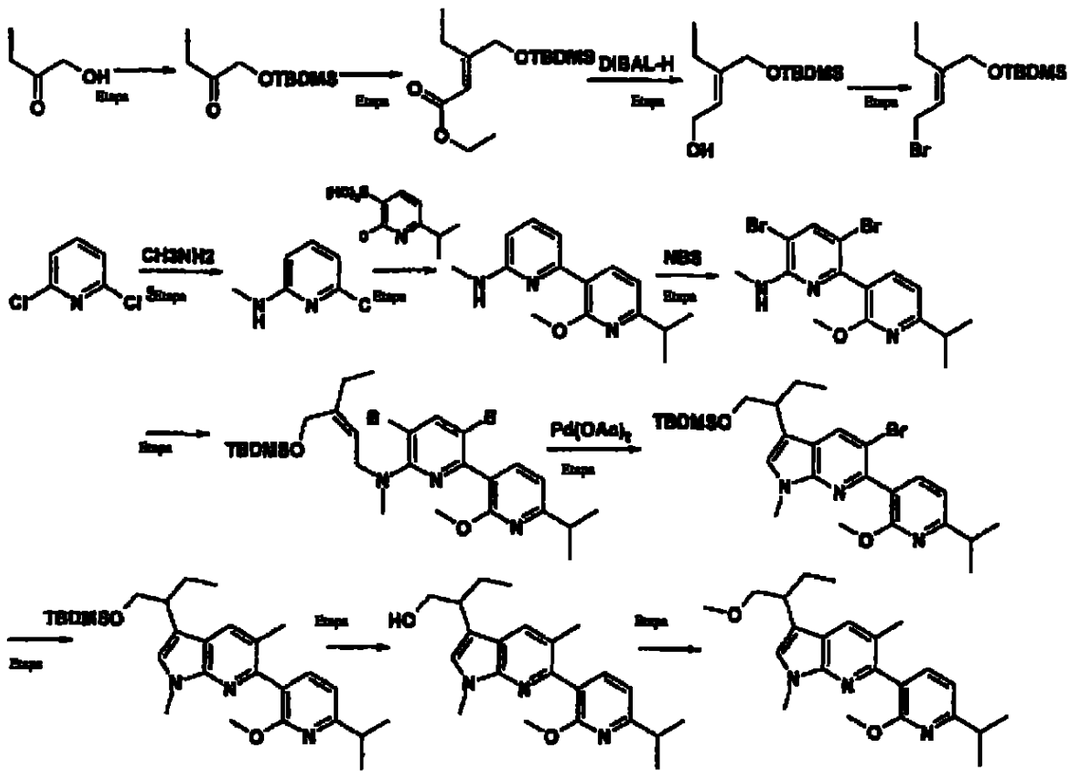
El compuesto alilo de Etapa B (100 mg) $Pd(OAc)_2$ (10 mg) TBAB (116 mg) y K_2CO_3 (132 mg) se disuelven en DMF (2 ml) se desgasifica y se calienta a 80 C durante la noche La mezcla se diluye con EtOAc y se lava con H_2O solución salina y se secan sobre $MgSO_4$ La purificación sobre gel de sílice produjo el producto Heck

Etapa D

El producto Heck de la Etapa C el previamente descrito ácido 2 metoxi-4-trifluorometoxifenil borónico y $Pd(PPh_3)_4$ se disuelven en tolueno Después de adición de Na_2CO_3 de 2N la mezcla de reacción se desgasifica y luego se calienta a 85 C durante la noche Posteriormente la solución se diluye con EtOAc y se lava con NaOH 2N H_2O y solución salina antes de ser secada sobre $MgSO_4$ La purificación sobre gel de sílice produjo el compuesto del título ^1H RMN ($CDCl_3$ δ ppm) 7 73 (1H s) 7 39 (en d J= 8 2 Hz) 6 95 (1H s) 6 93 (1H d J= 8 2 Hz) 6 82 (1H s) 3 81 (6H brs) 2 59 (1H m) 1 68-1 79 (4H m) 0 84 (6H t J= 7 3Hz)

EJEMPLO 49

Síntesis de 6-(6-isopropil 2-metoxi piridin-3-il)-3-(1-metoximetil propil) 1 5 dimetil 1H-pirrolo[2 3-b]piridino



Etapa A

Se agrega TBDMSCl (20g) a una solucón (0 C) de 4-hidroxi 2 butanona (17 6g) DMAP (200 mg) imidazol (10 8g) en DMF (160 ml) La mezcla de reacción se calienta naturalmente a temperatura ambiente y agita durante 24 horas La mezcla de reacción se agrega con agua y se extrae con acetato de etilo y se seca con Na_2SO_4 La purificación por columna con hexano/acetato de etilo da el producto Rf 0 4 (hexano/acetato de etilo 8 1)

Etapa B

Tnetil fosfonoacetato (17 3 ml) se agrega como una solución de THF (30 ml) una (0 C) suspensión fría de NaH (0 131mol) en THF anhidro (80 ml) La mezcla resultante se agita a 0 C durante 1 hora antes se agrega cetona (17 67g) como una solución de THF (10 ml) La reacción se continua a temperatura ambiente durante otras 2 horas Se agrega NH_4Cl acuoso saturado cuidadosamente y se separa La capa acuosa se extrae con éter Las capas orgánicas combinadas se lavan con agua solución salina La purificación por columna con hexano/acetato de etilo da el producto Rf 0 4 (hexano/acetato de etilo 15 1)

Etapa C

El material de partida (21 3g) se trata con DIBAL H (1 0M en tolueno 196 ml) a 0 C durante 6 horas Se agrega cuidadosamente agua para apagar el exceso de DIBAL La mezcla de reacción se filtra y se lava con acetato de etilo El filtrado se concentra para producir el producto crudo Rf 0 4 (hexano/acetato de etilo 3 1)

Etapa D

El material de partida (8 75g) se pone en cloruro de metileno anhidro (110 ml) se agrega trietilamina La mezcla resultante se enfría a 40 C Se agrega MsCl en forma de gotas y la reacción se continúa durante 1 hora a -40 C se agrega antes LiBr (13 2g) como una solución de THF (120 ml) La mezcla resultante se calienta naturalmente a temperatura ambiente y se continua durante 1 hora La reacción se apaga con agua y se separa La capa acuosa se extrae con éter Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 El producto crudo se puede utilizar durante la siguiente etapa de reacción sin purificación adicional Rf 0 4 (hexano/acetato de etilo 20 1)

Etapa E

2 6-dicloropirídino (17g) y solución acuosa de CH_3NH_2 (40% 26 8g) se colocan en THF (100 ml) en un tubo sellado y se calienta a 80 C durante 24 horas La reacción se enfría a temperatura ambiente y se diluye con agua La mezcla resultante se separa y se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 El producto crudo se utiliza durante la siguiente etapa de reacción sin purificación adicional LCMS 143 3 (M+H)

Etapa F

Una mezcla de 2 cloro-6-metilamino-pirídino (3 56 0 025mol)) ácido 2-metoxi-6-isopropil 3 piridilborónico (6 33g) $Pd(PPh_3)_4$ (577 mg) solución acuosa de Na_2CO_3 (1 0M 50 ml) y tolueno (50 ml) se calienta durante la noche a 100 C bajo una atmósfera de dinitrógeno La mezcla de reacción se enfría a temperatura ambiente y se separa La capa acuosa se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 El producto crudo se utiliza durante la siguiente etapa de reacción sin purificación adicional Rf 0 4 (hexano/acetato de etilo 4 1)

Etapa G

El material de partida crudo se pone en $CHCl_3$ anhidro (100 ml) 4 0 equivalente de NBS se agregan en una porción a 0 C La reacción se completa en 0 5 horas La mezcla de reacción se lava con agua y se seca con Na_2SO_4 Se purifica por

columna flash con hexano/acetato de etilo y da el producto como aceite claro LCMS m/z 496 1 (M+H)

Etapa H

NaH (795mg 60% en aceite mineral) se agrega a una solución de material de partida (6 34g) en DMF anhidro (100 ml) y se agita a temperatura ambiente durante 10 minutos Se agrega Bromuro (4 93g) preparado en la **Etapa D** en forma de gotas y la mezcla resultante se agita durante 3 horas La mezcla de reacción se apaga cuidadosamente con agua La mezcla resultante se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro Rf 0 4 (hexano/acetato de etilo 12 1)

Etapa I

Una mezcla de bromuro (9 26g) bromuro de tetrabutilamonio (5 95g) K_2CO_3 (6 12g) $Pd(OAc)_2$ (1 0g) en DMF (80 ml) se calienta a 80 C bajo atmósfera de N_2 durante 20 minutos La mezcla de reacción se enfría a temperatura ambiente y se diluye con agua La mezcla resultante se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro LCMS m/z 548 4 (M+H)

Etapa J

A una solución de t BuLi (1 7M/pentano 7 ml) en THF (30 ml) a 78 C se agrega una solución de bromuro (3 07g) en THF (5 ml) La mezcla resultante se agita a 78 C durante 10 minutos antes se agrega yodometano (1 4 ml) La reacción se

continúa durante 30 minutos La reacción cuidadosamente se apaga con EtOH La mezcla resultante se lava con agua y solución salina se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro Rf 0 4 (hexano/acetato de etilo 10 1)

Etapa K

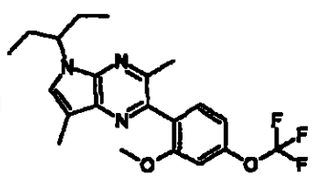
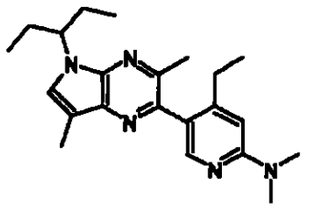
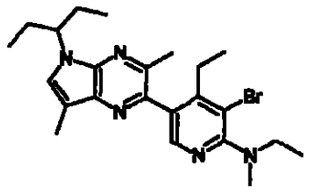
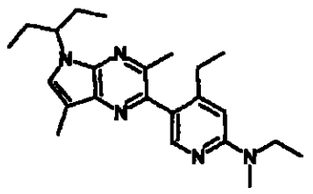
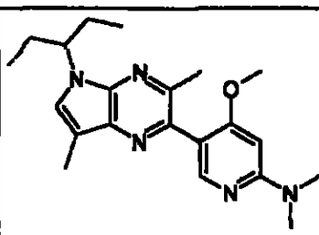
El material de partida (1 26g) se pone en THF (50 ml) seguido por la adición de fluoruro de tetrabutilamonio (1 5 equiv) a temperatura ambiente La reacción se completa después de 4 horas La mezcla de reacción se lava con agua solución salina y se seca con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto LCMS m/z 368 3 (M+H)

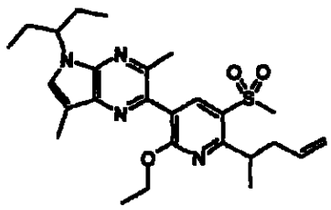
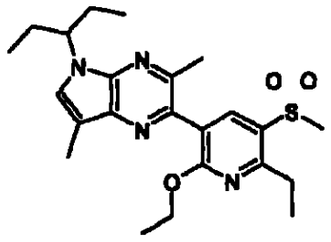
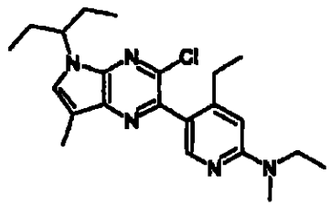
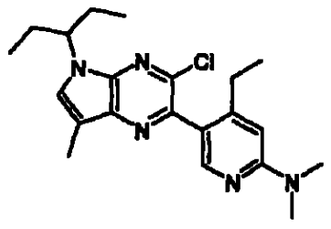
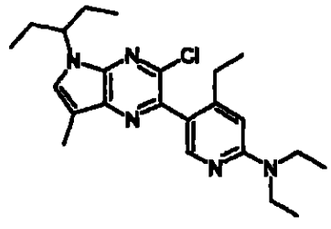
Etapa L

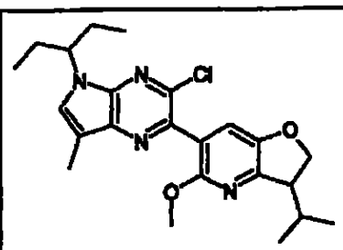
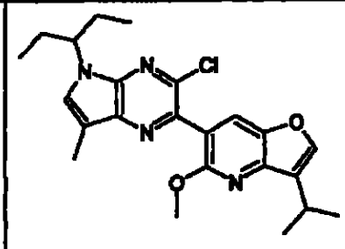
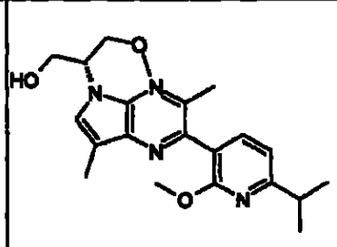
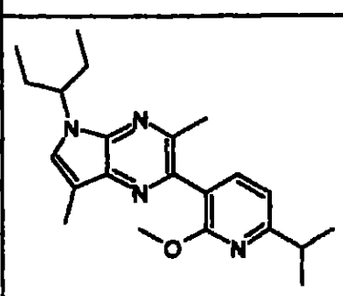
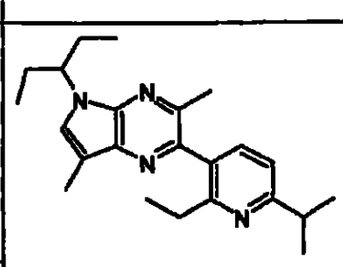
El material de partida (100 mg) se pone en DMF anhidro (4 ml) se agrega NaH (52mg 60%) seguido por la adición de CH_3I (5 equiv) La reacción se continúa durante la noche La reacción se apaga con agua y se extrae con acetato de etilo Las capas orgánicas combinadas se lavan con solución salina y se secan con Na_2SO_4 La purificación por columna flash con hexano/acetato de etilo da el producto como aceite claro LCMS m/z 382 3 (M+H)

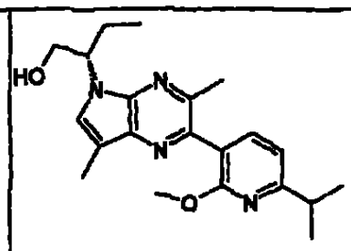
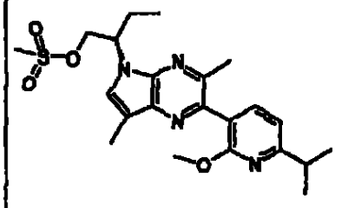
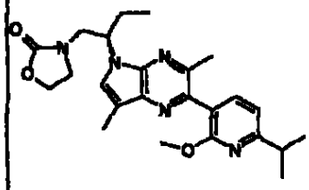
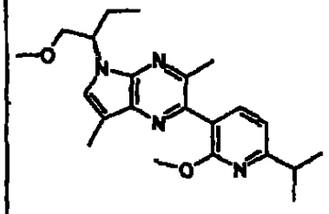
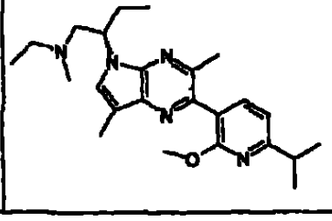
EJEMPLO 50

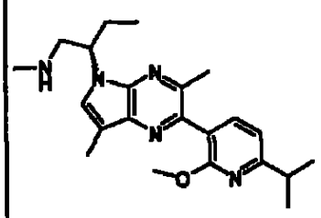
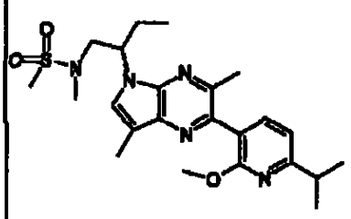
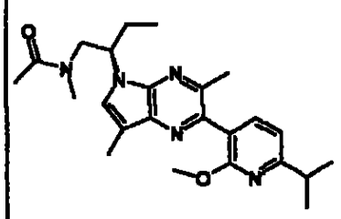
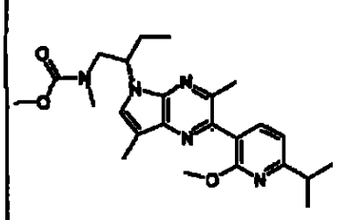
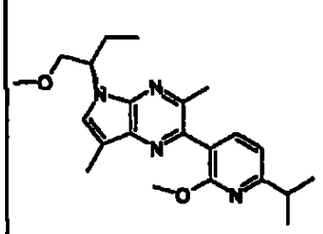
Los compuestos mostrados en la tabla se preparan análogamente de acuerdo con los procedimientos dados en los anteriores esquemas e ilustrados adicionalmente en los ejemplos anteriores

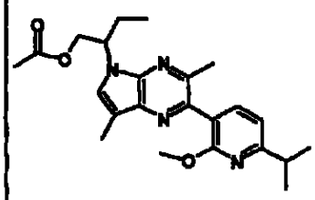
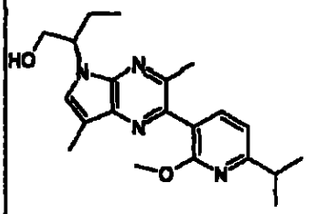
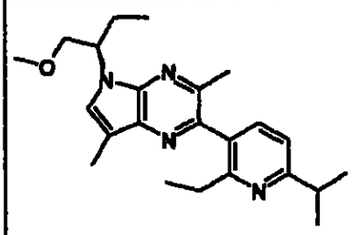
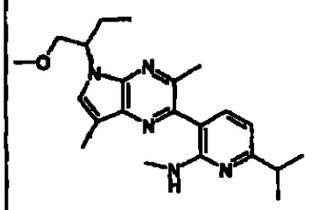
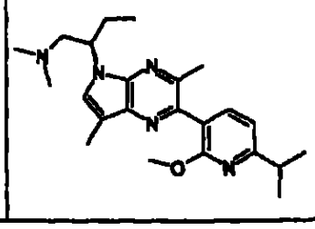
COMP #	ESTRUCTURA	NOMBRE COMPUESTO	MS, m/z	Rt(min)
101		5-(1 Etil-propil)-2 (2-metoxi-4-trifl rometoxi-fe il)-3 7-dimetil-5H-pirrolo [2 3 -b]pirazl	408.21	1 77
102		{4-Etil-5-[5-(1-etil-propil)-3 7 2-dimetil-5H-pirrolo [2,3 b]pirarzin 2-il] piridin-2 il}-dimetil-aml	366.22	1 41
103		{3-Bromo-4-etil-5-[5-(1-etil-propil)-3 7 dimetil-5H pirrol [2 3-b]pirazl 2 il}-piridin-2 il}-etil-metil-ml	458 12	1 94
104		Etil-(4-etil-5-[5-(1 etil-propil)-3 7 dimetil-5H pirrolo[2 3-b] pirazin-2-il] p ridin-2-il} metil-aml	380.23	1 66
105		{5-[5-(1-Etil-propil)-3 7-dimetil-5H-pirrolo[2 3-b] pirazl 2 il]-4-metoxi piridin-2-il}-dimetil-ml	368 19	1.39

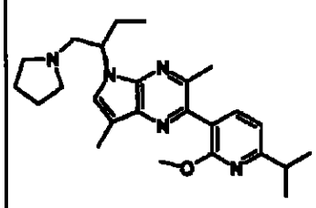
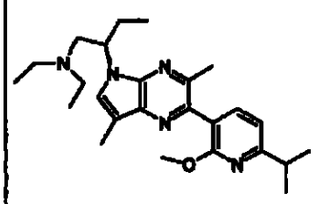
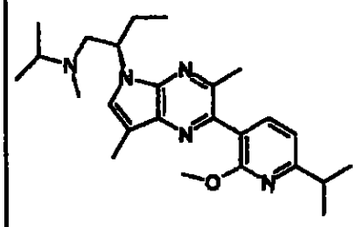
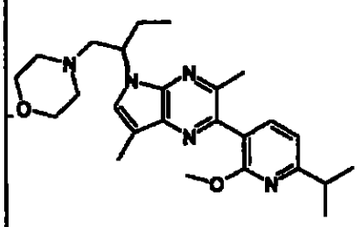
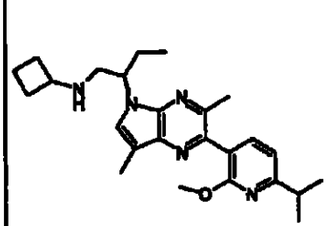
106		2-[2 Etoxi-5-metanos lfo il-6-(1 metil-but-3-en il)-piridin-3-il]-5-(1 -etil-propil)-3 7 dimetil-5H pirrolo[2 3-b] pirazina	485 17	1.82
107		2-(2 Etoxi-6-etil-5-metanos lfo l-piridin-3-il)-5-(1 etil-propil)-3 7 dimetil-5H-pirrolo[2 3-b] pirazina	445 16	1 74
108		{5-[3-Cloro-5-(1 etil-propil)-7-metil-5H-pirrolo[2 3-b]pirazin-2-il]-4-etil-piridi -2-il}-etil-metil-aml	399 96	1 50
109		{5-[3-Cloro-5-(1 etil-propil)-7-metil-5H-pirrol [2 3-b]pirazin-2-il]-4-etil-piridl -2-il}-d metil-am	386.20	1 48
110		{5-[3-Cloro-5-(1 etil-propil)-7-metil-5H-pirrolo[2 3-b]pirazin-2-il]-4-etil pirid n-2-il}-dietil-ml	414.23	1.51

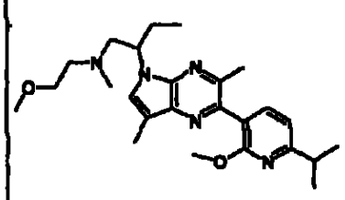
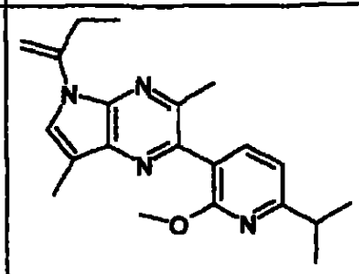
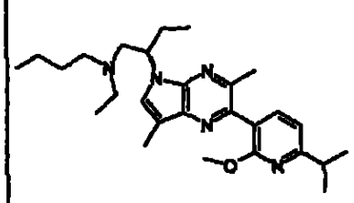
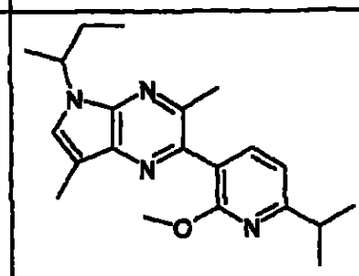
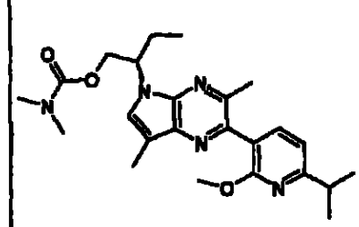
111		3-Cloro-5-(1-etil-propil)-2-(3-isopropil-5-metoxi-2 3-dihidro-furo[3 2-b]piridin-6-il)-7 metil-5H-pirrolo[2 3-b]pirazi	429 08	1 53
112		3-Cloro-5-(1-etil propil)-2-(3-isopropil-5-metoxi-2 3-dihidro-furo[3 2 b]piridin-6-il)-7 metil-5H-pirrol [2 3-b]pirazina	427 12	1 52
113		(R)-2-[2-(6-isopropil-2-metoxi-piridin-3-il)-3 7-dimetil-pirrolo[2 3-b]pirazin-5-il]-3-metoxi propa 1-ol	385 5	
114		5-(1 Etil-propil)-2-(6-isopropil-2 metoxi-piridl -3-il)-3 7-dimetil-5H pirrolo[2 3-b]pirazi	367 5	
115		2-(2 Etil-6-isopropil-piridin-3-il)-5-(1 etil-propil)-3 7 dimetil-5H pirrolo[2 3-b]pirazi	365 5	

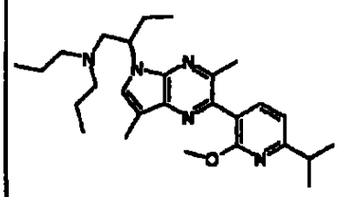
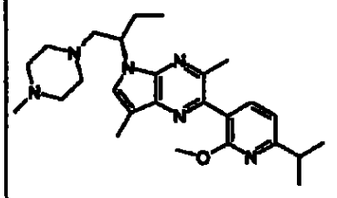
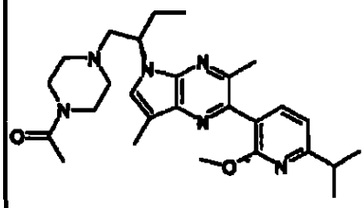
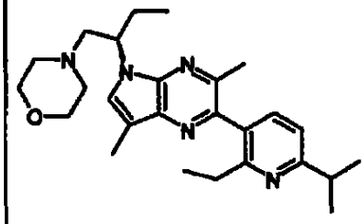
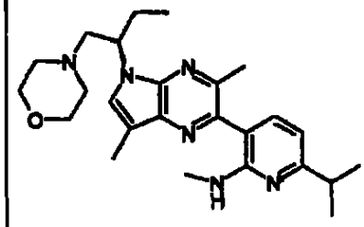
116		2-[(S)-2-(6-Isopropil-2-metoxi-piridin-3-il)-3 7-dimetil-pirrolo[2 3-b]pirazin-5-il]-butan-1-ol	369 4	
117		Éste d butilo d Ácid meta lfónico 2-[(S)-2-(6-Isopropil-2 metoxi-piridi -3-il)-3 7-dimetil-pirrolo[2 3-b]pira in-5-il]	447.4	
118		3-[2-[(S)-2-(6-Isopropil 2-metoxi-piridin-3-il)-3 7 d metil pirrolo[2,3-b]pirazin-5-il]-butil}-oxazolidi 2-o	438.4	
119		(S)-2-(6-Isopropil-2 metoxi-piridi -3-il)-5-(1-metoximetil propil)-3 7-dimetil-5H p rrol [2 3-b]pirazi	383.2	
120		Etil-{2-[(S)-2-(6-Isopropil-2-metoxi-piridi -3-il)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il]-butil}-metil-ami	410 4	

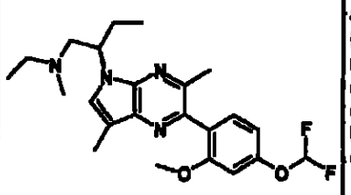
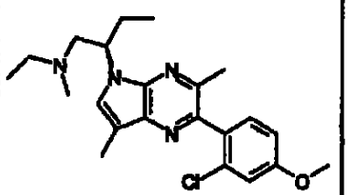
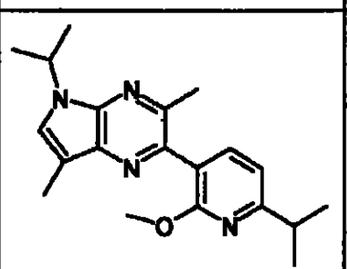
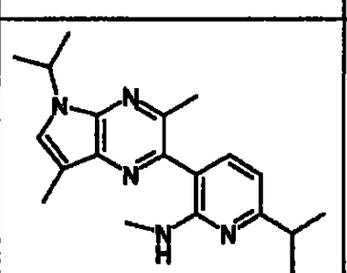
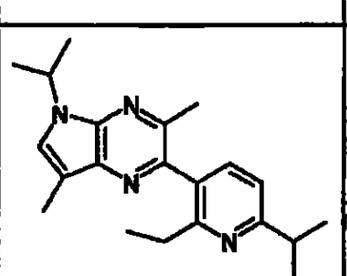
121		{2-[(S)-2-(6-Isopropil-2-metoxi-piridi -3-il)-3 7-dimetil pirrol [2 3-b]pirazin-5-il]-butil}-metil-ami	382.3	
122		N-{2-[(S)-2-(6-Isopropil-2-metoxi piridin-3-il)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il]-butil}-N-metil-Meta os ifon mid	460.3	
123		N-{2 [(S)-2-(6-Isopropil-2 metoxi-piridin-3-il)-3,7 dimetil pirrol [2 3-b]p razin-5-il] b til}-N metil-acetamid	424 5	
124		Éster d metilo de Ácido carbámico {2-[(S)-2-(6-Isopropil-2-metoxi-piridin-3-il)-3 7-dimetil-pirrol [2 3-b]pirazin-5-il]-butil}-metil	440.4	
125		(R)-2-(6-Isopropil-2 metoxi-piridi -3-il)-5-(1-metoximetil-propil)-3 7-dimetil-5H-pirrolo[2 3-b]pirazina	383 3	

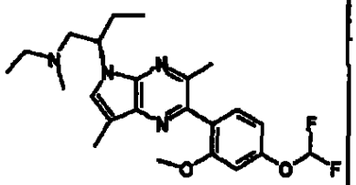
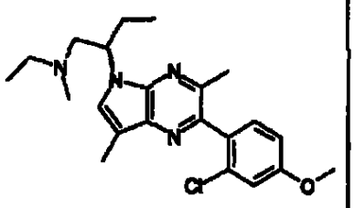
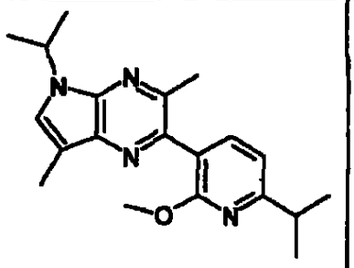
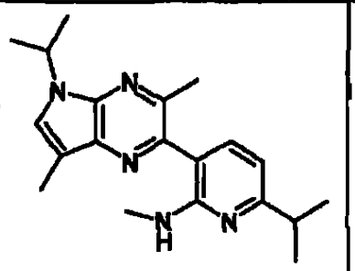
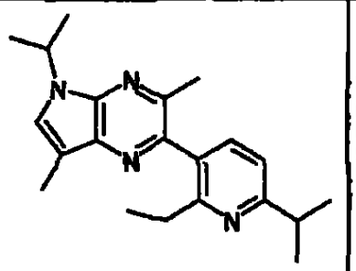
126		Éste de butilo d Ácid cético 2 [(R)-2 (6-isopropil-2-metoxi-piridin-3-il)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il]	411 4	
127		2 [(R)-2-(6-isopropil-2-metoxi-piridin-3-il)-3 7-dimetil-pirrol [2 3-b]pirazi 5-il]-buta 1-ol	369 4	
128		(R)-2-(2-Etil-6-isopropil-piridin-3-il)-5-(1 metoximetil-propil)-3 7-dimetil-5H-p rrolo[2 3-b]pirazi	381 4	
129		{6-Isopropil-3-[(R)-5-(1-metoximetil-propil)-3 7-dimetil-5H-pirrolo[2 3 b]pirazi -2-il]-piridin-2 il}-metil-ami	382 3	
130		{2 [(R)-2-(6-isoprop l 2 metoxi-piridi -3-il)-3 7-dimetil pirrolo[2 3-b]pirazin-5-il]-butil}-dimetil-mi	396 4	

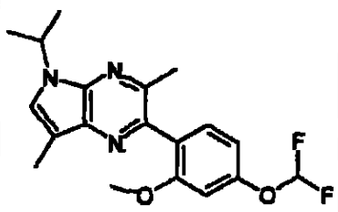
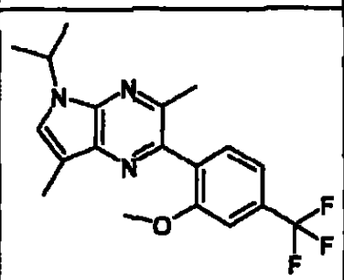
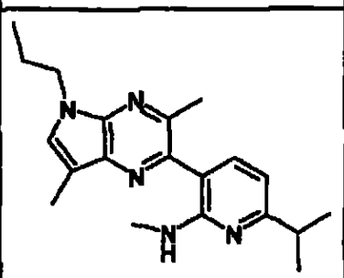
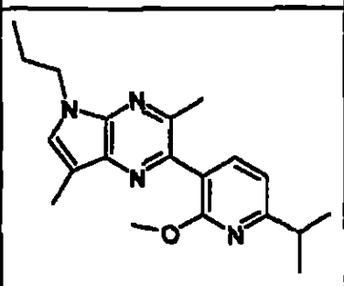
131		(R)-2-(6-isopropil-2 metoxi-piridin-3-il)-3 7-dimetil-5-(1 pirrolidin-1-ilmetil propil)5H-pirrolo[2 3-b]pirazina	422.2	
132		Dietil-{2-[(R)-2-(6-isopropil-2-metoxi-p ridin-3-il)-3 7 dimetil pirrol [2 3-b]pirazin-5-il] butil}-ami	424 1	
133		Isopropil-{2-[(R)-2-(6-isopropil-2-metoxi-piridin-3-il)-3 7 d metil-pirrol [2 3-b]pirazin-5-il] butil}-metil-mi	424 3	
134		(R)-2-(6-isopropil-2 metoxi-piridin-3-il)-3 7-dimetil-5-(1 m rfolin-1-ilmetil-propil)5H-pirrolo[2 3-b]pirazina	438.5	
135		Ciclob til-[2 [(R)-2 (6-isopropil-2 metoxi-piridin-3-il)-3 7-dimetil-pirrolo[2 3-b]pirazin-5- l]-butil}-ami	422.5	

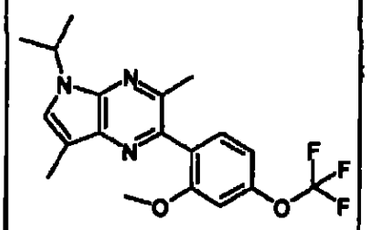
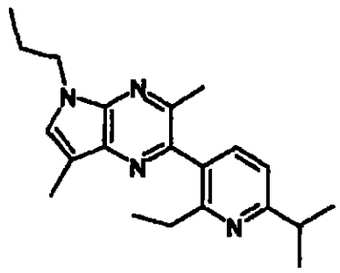
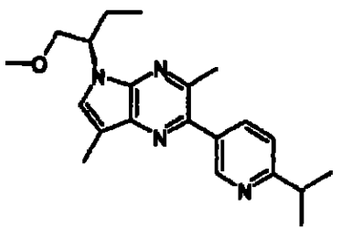
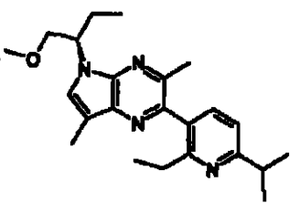
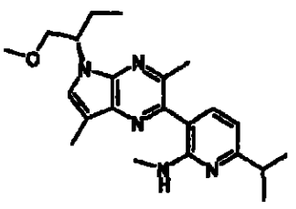
136		{2-[(R)-2-(6-Isopropil-2 metoxi-piridi -3-il)-3 7-dimetil pirrolo[2 3-b]pirazin-5-il]-butil}-(2 metoxi etil)-metil-m	440 4	
137		2 (6-Isopropil-2 metoxi piridin-3-il)-3 7-dimetil-5-(1 metileno-propil)-5H pirrolo[2 3-b]p razina	351.4	
138		Butil-etil-[2-[(R)-2_ (6-Isopropil 2 metoxi-piridi -3-il)-3 7-dimetil-pirrolo[2 3-b]pirazi 5-il]-butil}- mi	452.5	
139		5-sec-Butil-2-(2-6-Isopropil-metoxi-piridi -3-il)-3 7 -dimetil-5H pirrolo[2 3-b]pirazi	353.4	
140		Éste d butilo d Ácido dimetil carbámico 2 [(R)-2-(6-Isopropil-2-metoxi-piridin-3-il)-3 7 dimetil-pirrolo[2 3 -b]pirazin-5-il]	440.4	

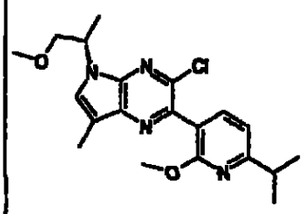
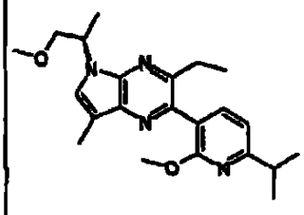
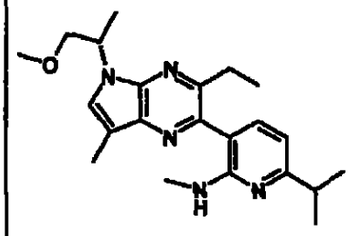
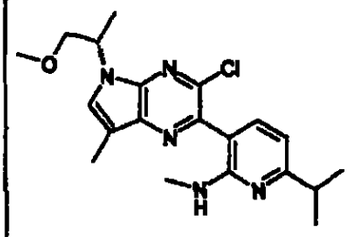
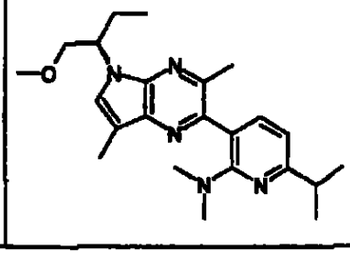
141		{2-[(R)-2-(6-Is propil-2 metoxi-piridin-3-il)-3 7-dimetil-pirrolo[2 3-b]pirazin-5-il]-butil}-dipropil-mina	452 5	
142		2-(6-Isopropil-2 metoxi-piridi -3-il)-3 7-dimetil-5-[(R)-1 (4-metil piperazin-1 il)metil]-propil]-5H pirrolo[2 3-b]pirazina	451 5	
143		1-(4-((R)-2-[2-(6-Isopropil-2 metoxi-piridin-3-il)-3 7 dimetil pirrol [2 3-b]pirazin-5-il]-butil}-piperazin-1 il)-etanona	479.5	
144		2-(2 Etil-6-isopropil-piridin-3-il)-3 7 dimetil-5-((R)-1 m rfolin-4-il metil-propil)-5H pirrolo[2 3-b]pirazina	436 4	
145		3-[3 7-Dimetil-5-((R)-1-m rfolin-4-il metil-propil)-5H pirrolo[2 3-b]pirazin-2-il]-6-Isopropil-piridin-2-il}metil-amina	437.3	

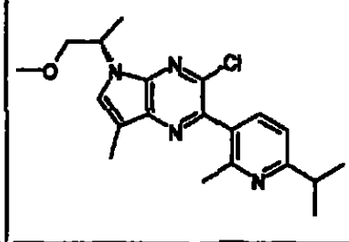
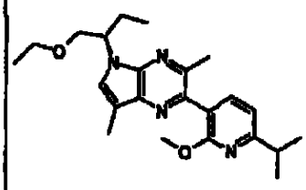
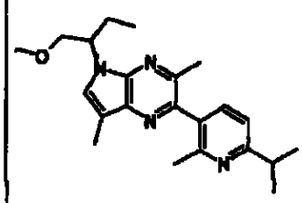
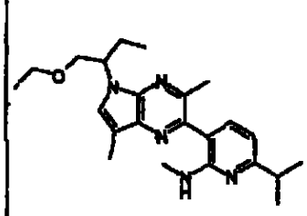
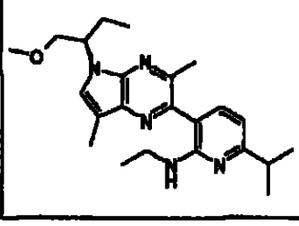
146		{(R)-2-[2(4-Difl rometoxi-2 met oxi-fenil)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il]-butil}-etil-metil-amina	433.5	
147		{(R)-2-[2-(2-Cloro-4-metoxi-fenil)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il] butil}-etil-metil-ami	401 5 403 5	
148		5-Isopropil-2-(6-isopropil-2-metoxi-piridin-3-il)-3 7 dimetil-5H pirrolo[2 3-b]pira ina	339 1	
149		[6-Isopropil-3-(5-isopropil-3 7-dimetil 5H-pirrol [2 3-b]pirazin-2-il)-piridin-2-il]-metil-ami	338.3	
150		2 (2-Etil-6-isopropil-piridin-3-il)-5-isopropil-3 7-dimetil-5H-pirrolo[2 3-b]pirazina	337.2	

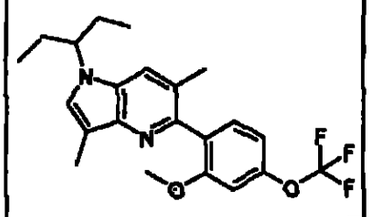
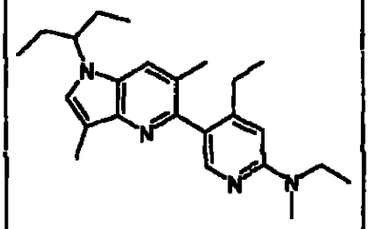
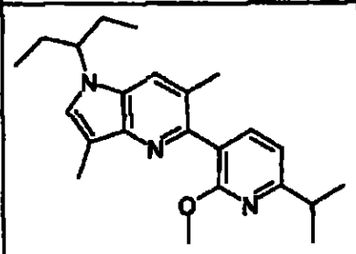
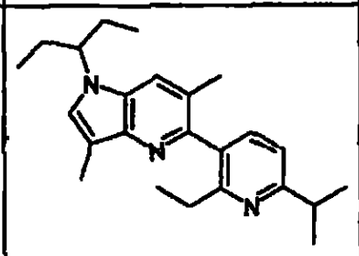
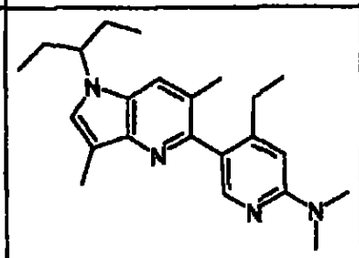
146		{(R)-2-[2(4-Difluorometoxi-2 met oxi fe il)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il]-butil}-etil-metil-ami	433.5	
147		{(R)-2-[2-(2-Cloro-4-metoxi-fenil)-3 7 dimetil-pirrolo[2 3-b]pirazin-5-il] butil}-etil-met l-ami	401 5 403 5	
148		5-Isopropil-2-(6-isopropil-2-metoxi-piridi -3-il)-3 7 d metil-5H pirrolo[2 3-b]pirazina	339 1	
149		5-Isopropil-2-(6-isopropil-2 metoxi-piridin-3-il)-3 7 dimetil-5H pirrolo[2 3-b]pira ina	338.3	
150		2-(2 Etil-6-isopropil-piridin-3-il)-5-isopropil-3 7-dimetil 5H pirrol [2 3-b]pirazina	337.2	

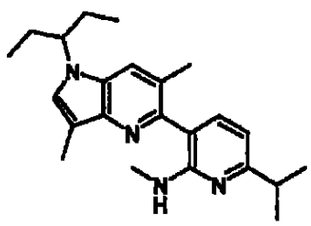
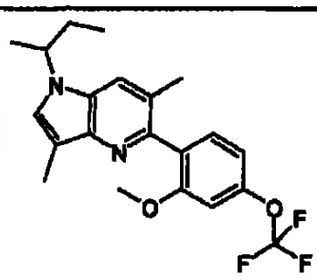
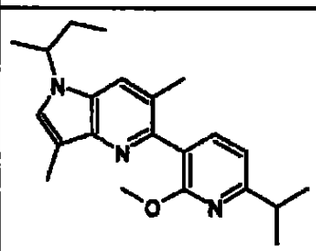
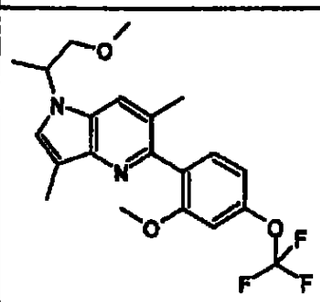
151		2-(4-Diftu rometoxi-2-metoxi-fe il)-5-isopropil-3 7-dimetil-5H-pirrolo[2 3-b]pirazi	362 1	
152		5-isopropil-2-(2 metoxi-4-trifl rometil-fe il)-3 7-dimetil-5H-pirrol [2 3-b]pirazi	364 1	
153		[3-(3 7 Dimetil-5-propil-5H-pirrolo[2 3-b]pirazin-2-il)-6-isopropil-piridi 2-il]-metil-ami	338 1	
154		2 (6-isopropil-2 metoxi piridin-3-il)-3 7-dimetil-5-propil-5H-pirrolo[2 3-b]pirazi	339 1	

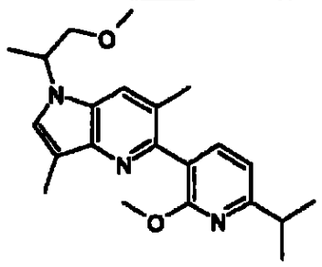
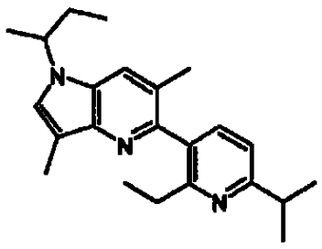
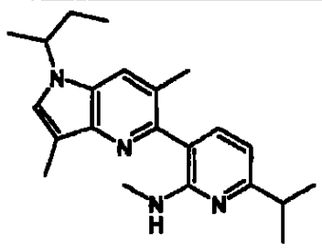
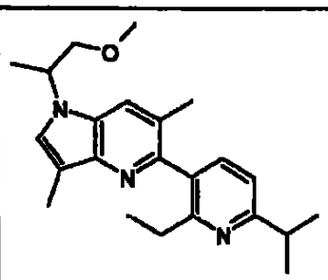
155		5-Isopropil-2-(2 metoxi-4-trifl orometoxi-fenil)-3 7-dimetil-5H-pirrolo[2 3-b]pirazi	380 0	
156		2-(2 Etil-6-isopropil-6 piridin-3-il)-3 7 dimetil-5-propil-5H-pirrol [2 3-b]pirazina	337.2	
157		(R)-2-(6-Is propil-piridin-3-il)-5-(1 metoximetil-propil)-3 7-dimetil-5H-pirrolo[2 3-b]pirazi	353 3	
158		(S)-2-(2-Etil-6-isopropil-piridin-3-il)-5-(1-metoximetil-propil)-3 7-dimetil-5H-pirrolo[2 3-b]pirazina	381 1	
159		{6-Isopropil-3-[(S)-5-(1-metoximetil propil)-3 7-dimetil-5H-pirrolo [2 3-b]pirazi -2-il]-iridin-2-il}-metil-mi	382.3	

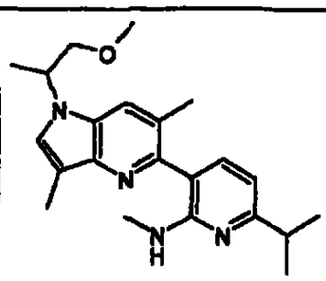
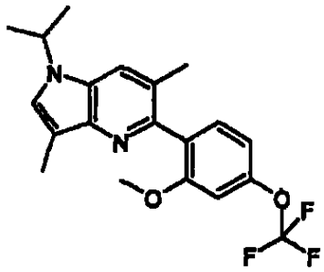
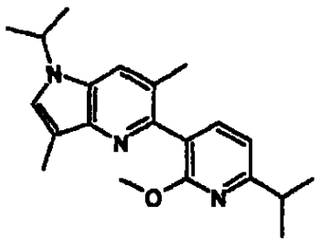
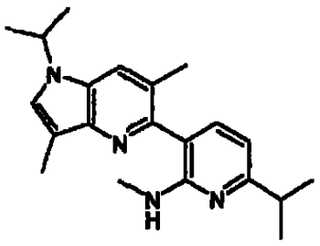
160		(S)-3-cloro-2-(6-isopropil-2-metoxi-piridin-3-il)-5-(2 metoxi-1-metil etil)-7-metil-5H-pirrolo[2 3-b]pirazina	389 4 391 4	
161		(S)-3-Etil-2-(6-isopropil-2 metoxi-piridin-3-il)-5-(2-metoxi-1 metil-etil)-7-metil-5H-pirrolo[2 3-b]pira ina	383 4	
162		{3-[3-Etil-5-((S)-2 metoxi-1-metil etil)-7-metil-5H-pirrolo[2 3-b]pirazin-2-il]-6-isopropil-piridi 2-il}-metil-ami	382.4	
163		{3-[3-Cloro-5-((S)-2 metoxi 1-metil-etil)-7-metil-5H-pirrol [2 3-b]pirazi 2-il]-6-i propil-piridin-2 il)-metil-am	388.4 390.4	
164		{6-Isopropil-3-[5-((R)-1 metoximetil-propil)-3 7-dimetil-5H-pirrolo [2 3-b]pirazin-2 il]-piridin-2 l}-dimetil-mina	396 5	

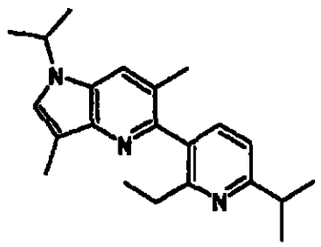
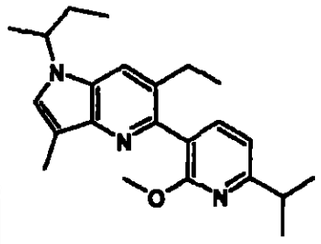
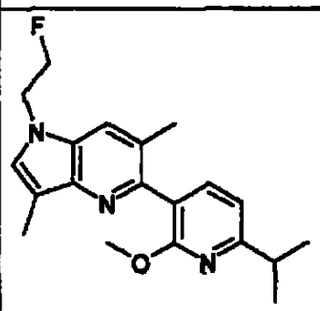
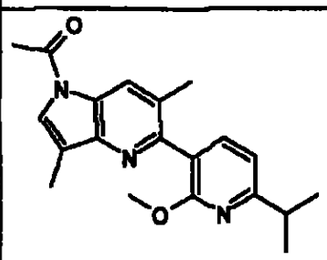
165		3-Cloro-2-(6-isopropil-2 metil-piridin-3-il)-5-((S)-2 metoxi-1-metil-etil)-7-metil-5H pirrolo[2 3-b]pirazi	373.3 375.3	
166		5-((R)-1-Etoximetil-propil)-2-(6-isopropil-2 metoxi-piridi -3-il)-3 7-dimetil-5H pirrolo[2 3-b]pira ina	397.5	
167		2-(6-Isopropil-2 metil-piridin-3-il)-5-((R)-1-metoximetil propil)-3 7-dimetil-5H-pirrolo[2 3-b]pirazi	367.5	
168		{3-[5-((R)-1 Etoximetil-propil)-3 7-dimetil-5H-pirrolo[2 3-b]pirazi 2 il]-6-isoprop i-piridin-2-il-metil-mi	396.5	
169		Etil-(6-isopropil-3-[5-((R)-1 metoximetil-propil)-3 7-dimetil-5H pirrolo[2 3-b]pirazin-2 il]-piridin-2 il)-ami	396.5	

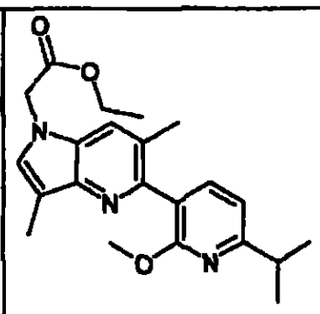
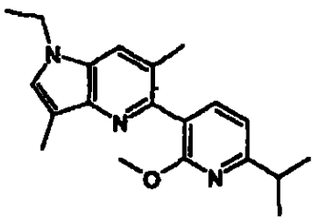
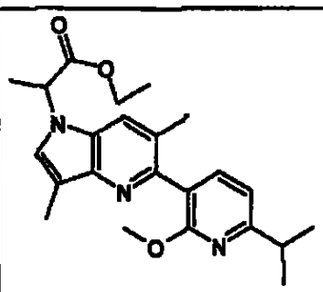
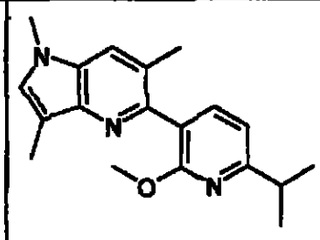
170		1-(1 Etil-propil)-5-(2-metoxi-4-trifl orometoxi-fe il)-3 6-dimetil-1H-pirrolo[3,2 b]piridina		
171		Etil-(4-etil-5-[1-(1 etil-propil)-3 6-dimetil 1H pirrolo[3 2-b]piridi 5-il]-piridi -2-il)-metil-amina	379 5	
172		1 (1 Etil-propil)-5-(6-isopropil-2 metoxi-piridi -3-il)-3 6-dimetil 1H pirrolo[3,2 b]piridi	366 4	
173		5-(2 Etil-6-isopropil-pirid n-3-il)-1-(1 etil-propil)-3 6-d metil-1H pirrolo[3 2-b]piridina	364.5	
174		(4-Etil-5-[1-(1-etil-propil)-3 6-dimetil 1H-pirrol [3 2 bipiridi -5-il]-piridin-2-il)-dimetil-amin	365.5	

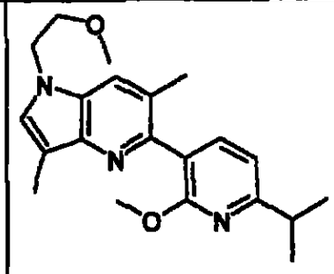
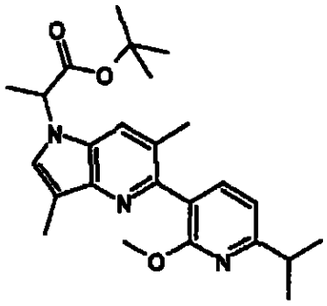
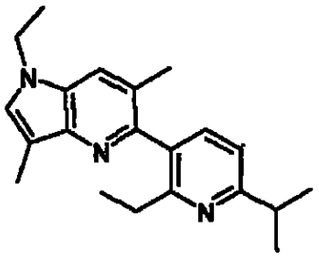
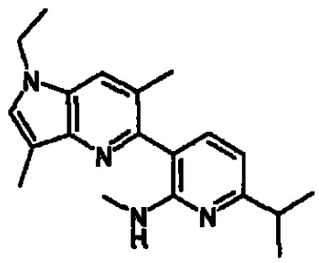
175		{3-[1-(1 Etil-propil)-3 6-dimetil-1H pirrolo[3,2-b]piridi -5-il]-6-isopropil-piridin-2-il]-metil-mi	365.5	
176		1-sec-Butil-5-(2 metoxi-4-trifl orometoxi-fe il)-3 6-dimetil-1H-pirrolo[3,2 b]piridina	393.3	
177		1-sec-Butil-5-(6-isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-1H pirrol [3 2-b]p ridi	352.4	
178		1 (2-Metoxi 1 metil-etil)-5-(2 metoxi-4-trifl rometoxi fe il)-3 6-dimetil-1H-pirrolo[3,2 b]piridi	409.3	

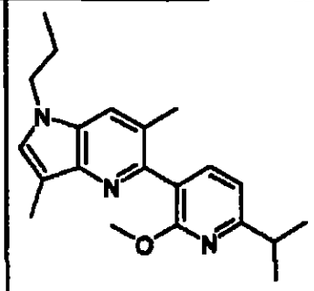
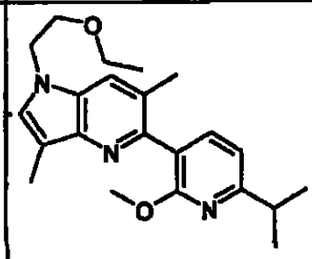
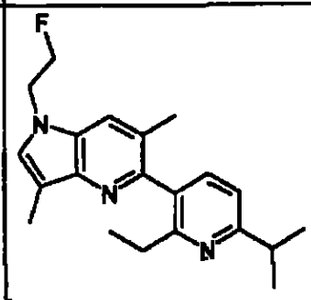
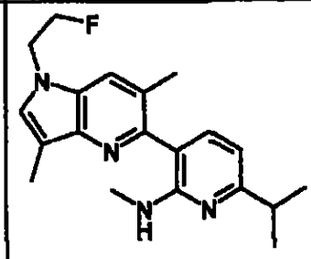
179		5-(6-Isopropil-2 metoxi-piridin-3-il)-1 (2-metoxi 1 metil-etil)-3 6-dimetil-1H pirrol [3 2-b]piridi	368 1	
180		1-sec-Butil-5-(2-etil-6-isopropil-piridin-3-il)-3 6-dimetil-1H pirrol [3 2-b]piridi	350 5	
181		[3-1-sec-Butil-3 6-dimetil-1H pirrolo[3 2-b]piridi 5-il)-6-isopropil-pirid -2-il]-metil-ami	351.4	
182		5-(2 Etil-6-isopropil-piridin-3-il)-1 (2-metoxi 1-metil-etil)-3 6-dimetil-1H-pirrolo[3 2 b]piridi	366 3	

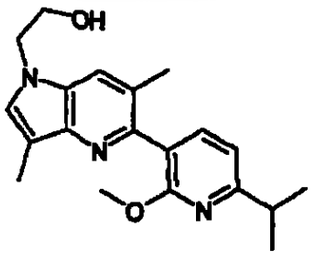
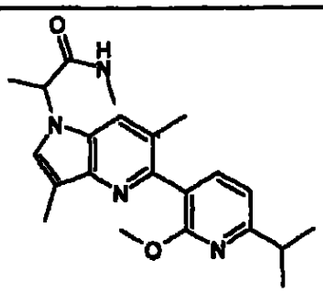
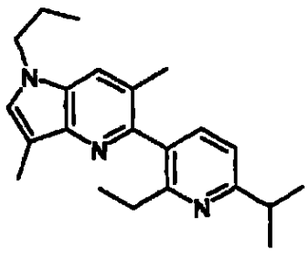
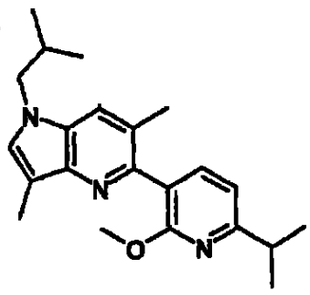
183		{6-Isopropil-3-(1-(2 metoxi-1-metil-etil)-3 6-dimetil-1H-pirrol [3 2-b]piridin-5-il}-piridin-2-il)-metil-mi	367.5	
184		1 Isopropil-5-(2 metoxi-4-trifluorometoxi-fe il}-3 6-dimetil-1H-pirrolo[3 2 b]piridina	379 4	
185		1 Isopropil-5-(6-isopropil-2-metoxi-piridin-3-il}-3 6-dimetil-1H-pirrolo[3 2-b]pirid	338.3	
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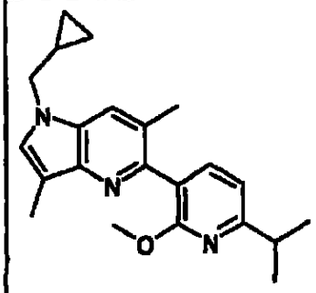
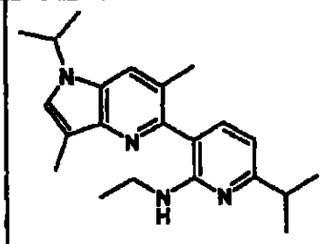
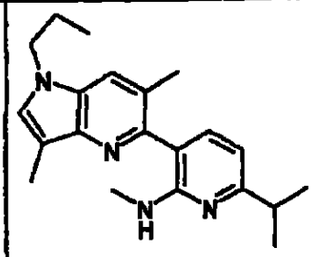
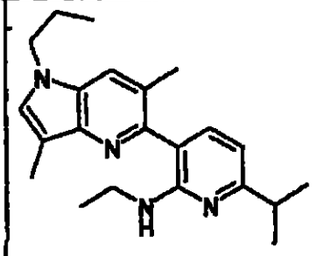
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188		1-sec-Butil-6-etil-5-(6-isopropil-2 metoxi-piridin-3-il)-3-metil-1H pirrolo[3 2-b]piridi	366 4	
189		1 (2-Fl oro-etil)-5-(6-isopropil-2-metoxi-piridin-3-1-il)-3 6-dimetil-1H-pirrolo[3 2-b]piridina	342.4	
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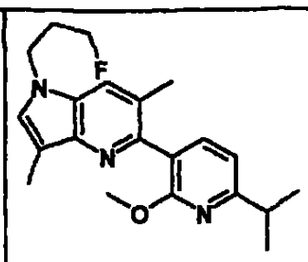
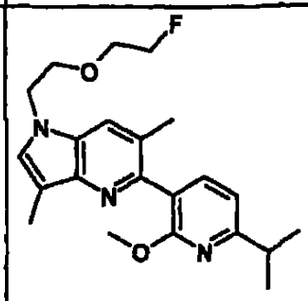
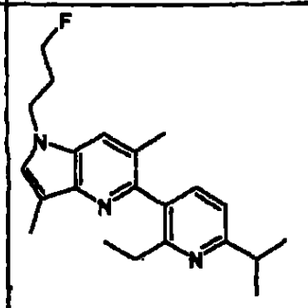
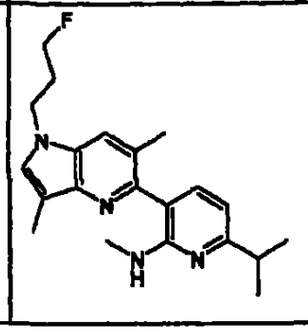
191		Éste etílico d Ácid [5-(6-isopropil -2-metoxi-piridi -3-il)- 3 6-dimetil- pirrolo[3 2-b]piridi 1 il]-acético	382.3	
192		Éster etílico d Ácido [5-(6-isopropil -2-metoxi-piridin-3-il)- 3 6-dimetil- pirrol [3 2-b]piridi 1 il]-acético	324.4	
193		Éster etílico d á id 2-[5-(6-isopropil- 2 metoxi-piridi -3-il)- 3 6-dimetil- pirrolo[3 2-b]piridin- 1-il]-propio ico	396.4	
194		5-(6-isopropil-2 metoxi-piridin-3-il)- 1 3 6-trimetil-1H pirrol [3 2 b]piridi	310 4	

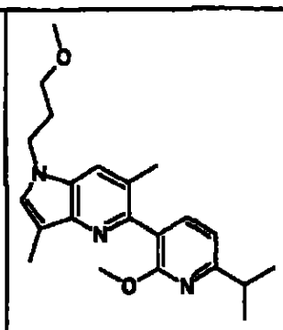
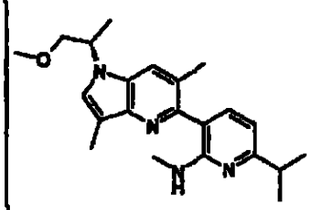
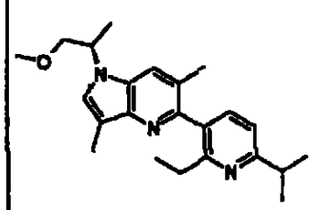
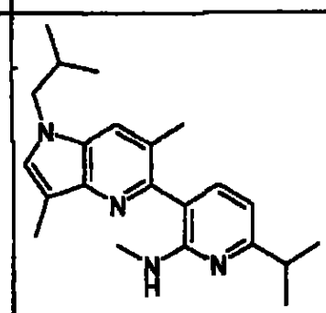
195		5-(6-isopropil-2 metoxi-piridin-3-il)-1-(2-metoxi-etil)-3 6-dimetil-1H pirrolo[3 2-b]pirid	354 1	
196		Éste terc-b tílico de ácid 2-[5-(6-isopropil-2-metoxi-pirid -3-il)-3 6-dimetil-pirrolo[3 2 b]piridi 1 il]-propiónico	424.3	
197		1 Etil-5-(2-etil-6-isopropil-pyridin-3-il)-3 6-dimetil-1H-pirrolo[3,2 b]piridi	322.5	
198		[3-(1 Etil-3 6-dimetil-1H pirrol [3 2-b]p ridin 5-il)-6-isopropil-piridin-2-il] metil-ami	323 5	

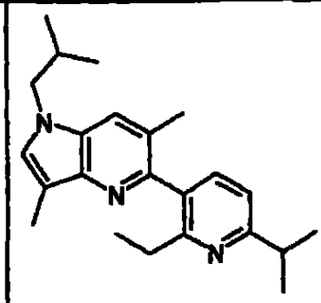
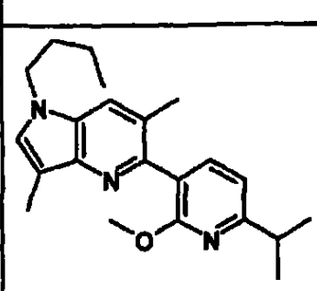
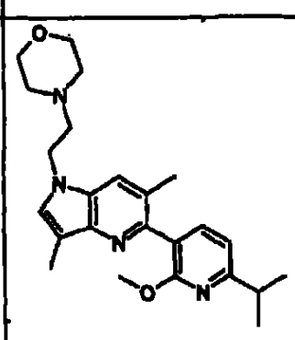
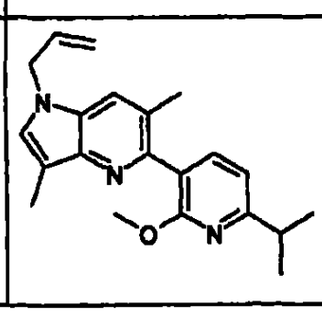
199		5-(6-isopropil-2 metoxi-piridin-3-il)-3 6-dimetil-1-propil-1H-pirrolo[3 2 b]piridi	338.4	
200		1-(2-Etoxi-etil)-5-(6-isopropil-2 metoxi-piridi -3-il)-3 6-dimetil-1 pirrolo[3 2-b]piridina	368.3	
201		5-(2 Eti6-isopropil-piridin-3-il)-1-(2 fl ro-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridina	340.2	
202		{3-[1-(2-Fluoro-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridi 5-il]-6-isopropil-piridin-2 il}-metil-ml	341.4	

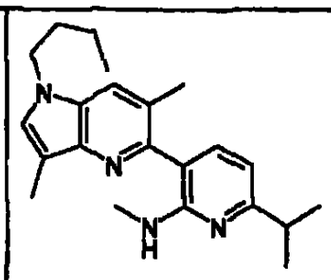
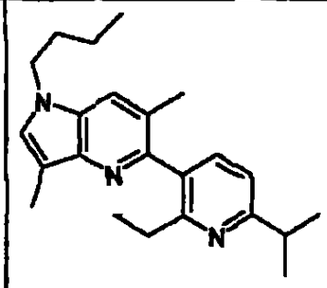
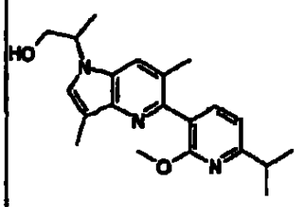
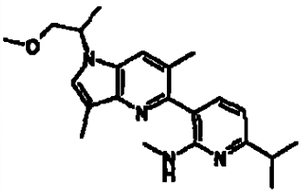
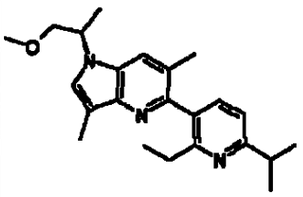
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204		2-[5-(6-Isopropil-2 metoxi-piridi -3-il)-3 6-dimetil-pirrolo[3 2-b]piridin-1-il]-N-metil-Propion mid	381 4	
205		5-(2-Etil-6-isopropil-piridin-3-il)-3 6-dimetil-1-propil-1H-pirol [3 2-b]piridi	336.4	
206		1 Isobutil-5-(6-isopropil 2-metoxi-piridin-3-il)-3 6-dimetil-1H pirrolo[3,2 b]piridi	352 4	

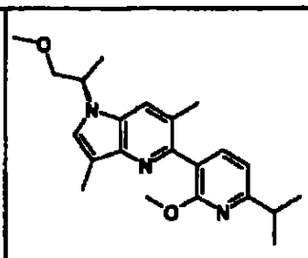
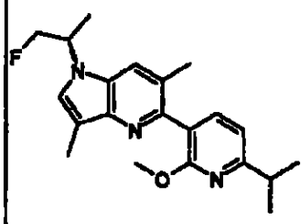
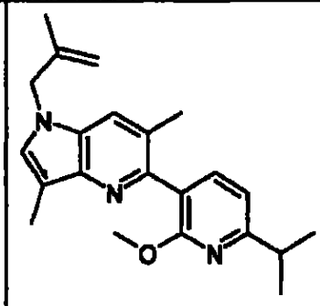
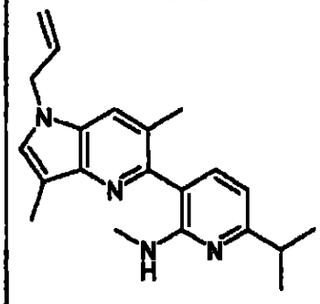
207		1-Ciclopropilmetil-5-(6-isopropil-2 metoxi-piridin-3-il)-3 6-dimetil-1H pirrolo[3 2-b]piridi)	350.4	
208		Etil-[6-isopropil-3-(1-isopropil-3 6-dimetil 1H pirrol [3 2-b]piridin-5-il)-piridi -2-il]-mi	351 4	
209		[3-(3 6-D metil-1 propil-1H pirrol [3 2 b]piridin-5-il)-6-is propil-piridin-2-il]-metil-ami	337 4	
210		[3-(3 6-Dimetil-1 propil-1H-pirrolo[3 2 b]piridi -5-il)-6-isopropil-pirid n-2-il]-etil-ami	351 5	

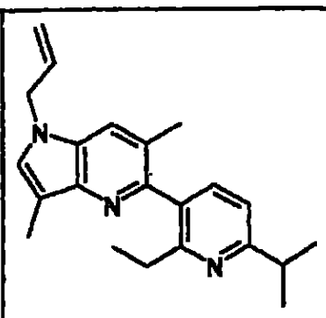
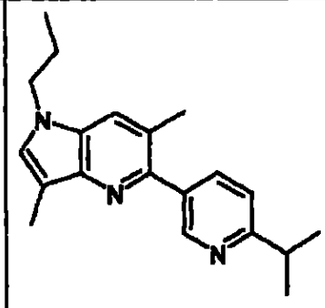
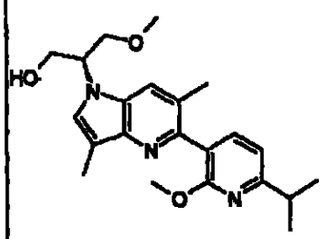
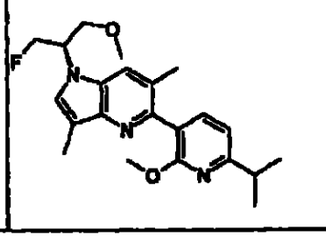
211		1-(3-Fl ro-propil)-5-(6-isopropil-2 metoxi-piridi 3-il)-3 6-dimetil-1H pirrolo[3 2-b]piridi	356.4	
212		1-[2-(2-Fl ro-etoxi)-etil]-5-(6-isopropil-2 metoxi-piridin-3-il)-3 6-dimetil-1H pirrolo[3 2-b]piridi	386 4	
213		5-(2-Etil-6-isopropil-piridin-3-il)-1-(3-fl oro-propil)-3 6-dimetil-1H-pirrolo[3,2 b]piridi	354.20	1.96
214		{3-[1-(3-Fluoro-propil)-3 6-dimetil-1H-pirrolo[3 2 b]piridin-5-il]-6-Isopropil-piridin-2-il}-metil-aml	355 19	1 79

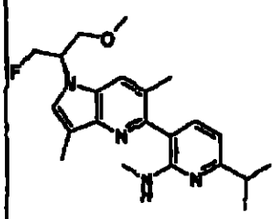
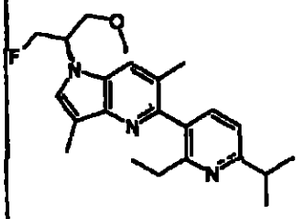
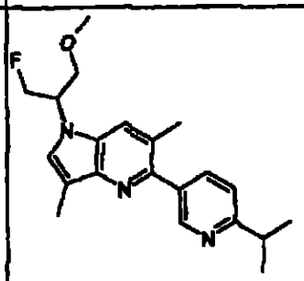
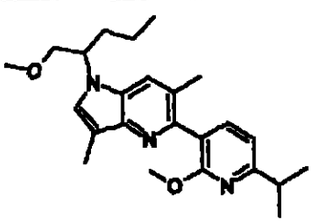
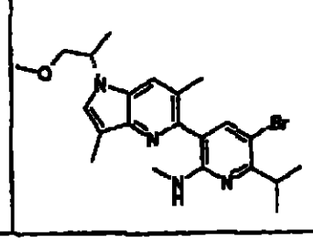
215		5-(6-Isopropil-2 metoxi-piridin-3-il)-1-(3-metoxi-propil)-3 6-dimetil-1H-pirrolo[3 2-b]piridi	368.4	
216		{6-Isopropil-3-[1-((S)-2-metoxi-1-metil-etil)-3 6-dimetil-1H pirrol [3 2 b]piridi -5-il]-piridi 2-il}-metil-am na	367.2	
217		5-(2-Etil-6-isopropil-piridin-3-il)-1-((S)-2 metoxi-1-metil-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridina	366.4	
218		[3-(1 Isobutil-3 6-dimetil-1H pirrolo[3 2 b]piridi 5-il)-6-is propil-piridi 2-il]-metil-m	351 5	

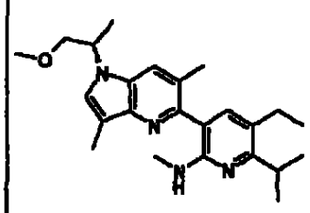
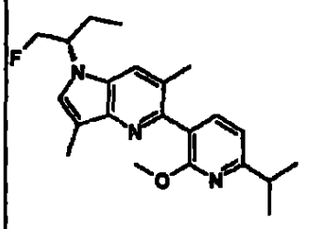
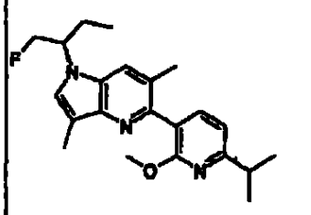
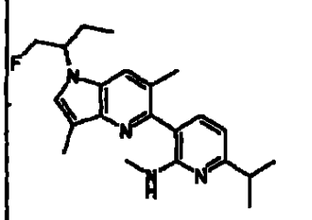
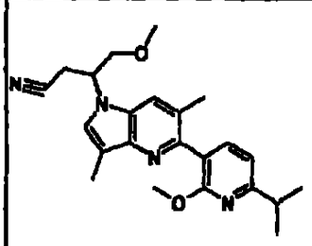
219		5-(2-Etil-6-isopropil-piridin-3-il)-1 isobutil-3 6-dimetil-1H pirrol [3 2 b]piridi	350.5	
220		1 Butil-5-(6-is propil-2 metoxi-piridi -3-il)-3 6-dimetil-1H pirrolo[3 2-b]piridi	352.4	
221		5-(6-isopropil-2 metoxi-piridi -3-il)-3 6-dimetil-1-(2 morfolin-4 il-etil)-1H-pirrolo[3 2 b]piridi	409.5	
222		1-Alil-5-(6-isopropil-2-metoxi-piridi -3-il)-3 6-dimetil 1H pirrolo[3 2-b]piridina	Rf 0 33 (Hexano Etilacetato 4 1)	

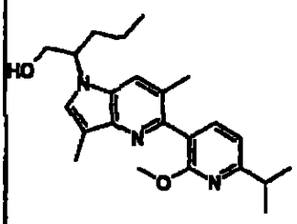
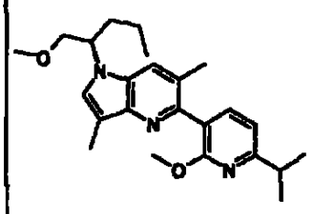
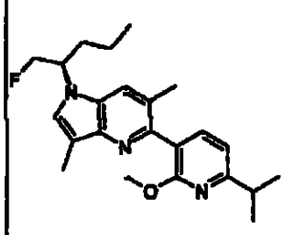
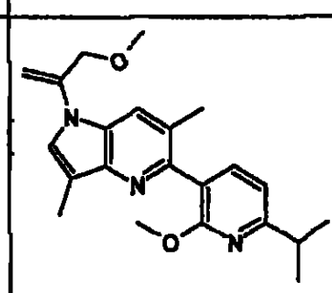
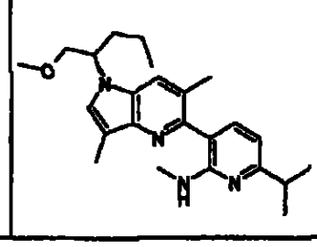
223		[3-(1-Butil-3 6-dimetil-1H-pirrolo[3 2-b]pirid -5-il)-6-isopropil piridin-2 il]-metil min	351 5	
224		1 Butil 5-(2-etil-6-isopropil-piridin-3-il)-3 6-dimetil-1H pirrol [3 2-b]piridi	350.5	
225		(R)-2-[5-(6-Isopropil-metoxi-piridin-3-il)-3 6-dimetil-pirrol [3 2-b]piridin-1 l]-propan-1-ol	354 4	
226		{6-Isopropil-3-[1-((R)-2-metoxi-1-metil-etil)-3 6-dimetil-1H-pirrolo[3,2 -b]piridin-5-il]-piridin-2-il}-metil-amina	367 5	
227		5-(2-Etil-6-isopropil-piridin-3-il)-1-((R)-2 metoxi-1-metil-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridina	366.4	

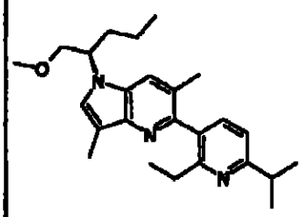
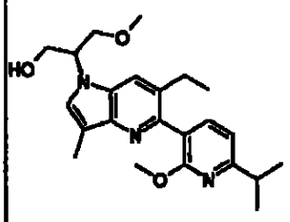
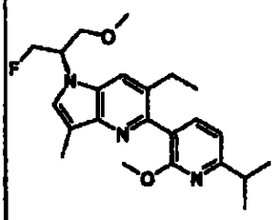
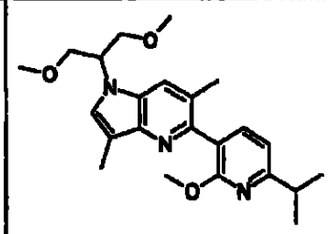
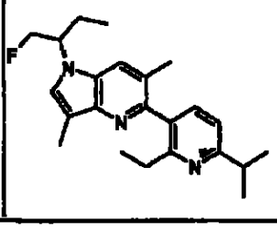
228		5-(6-Isopropil-2 metoxi-piridin-3-il)-(1-((R)-2-metoxi 1 metil-etil)-3 6-dimetil-1H-pirrolo[3 2-b]piridi	Rf 0.4 (Hexano Etil ce tato 2 1)	
229		1-(1-((R)-2 Fluoro-1 metil-etil)-5-(6-isopropil-2-metoxi-prpiridin-3-il)-3 6-dimetil-1H pirrol [3 2-b]piridi	356.4	
230		5-(6-Isopropil-2 metoxi piridi -3-il)-3 6-dimetil-1 (2 metil-alil)-1H-pirrolo[3 2-b]piridi	350.5	
231		[3-(1-Alil-3 6-dimetil-1H pirrolo[3 2-b]piridi 5-il)-6-isopropil-piridin-2-il]-metil-mina	335.3	

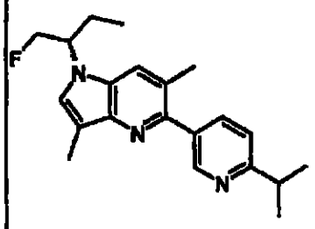
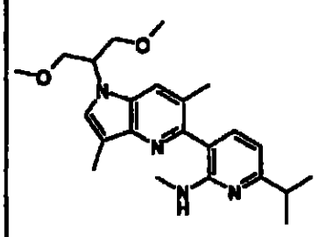
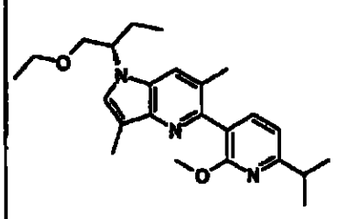
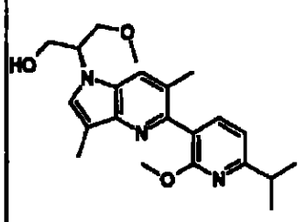
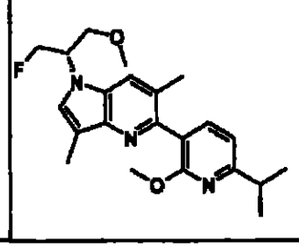
232		1-Alil-5-(2-etil-6-isopropil-piridin-3-il)-3 6-dimetil-1H pirrolo[3 2-b]piridi	334.4	
233		(S)-2-[5-(6-isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-pirrolo[3 2-b]piridi 1-il]-3-metoxi-propan-1-ol	308.3	
234		(S)-2 [5-(6 isopropil 2 metoxi-piridi -3-il)-3 6-dimetil pirrolo[3 2-b]piridin-1-il]-3-metoxi-propa 1-ol	Rf 0 3 (Hexano /etil Etil ce tato 1 1)	
235		1-((R)-1-Fluorometil-2 metoxi-etil)-5-(6-isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-1H pirrolo[3,2 b]piridi	386.6	

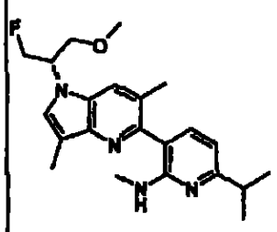
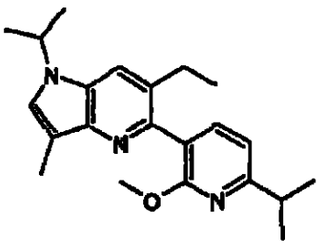
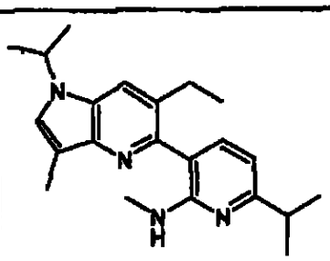
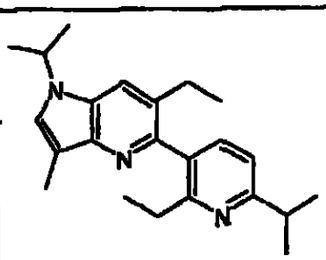
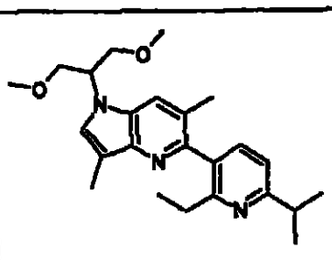
236		{3-[1-((R)-1 Fluorometil-2 metoxi-etil)-3 6-dimetil-1H-pirrol [3 2-b]piridi -5-il]-6-isopropil piridin-2-il}-metil- ml	385 5	
237		5-(2 Etil-6-isopropil-piridin-3-il)-1-((R)-1 fl rometil-2 metoxi-etil)-3 6-dimetil-1H-pirrolo[3 2-b]piridi	384.4	
238		1-((R)-1 Fluorometil-2-metoxi-etil)-5-(6-isopropil-piridin-3-il)-3 6-dimety]-1H pirrolo[3 2-b]piridina	356 4	
239		5-(6-Isopropil-2 metoxi-piridin-3-il)-1-(1 metoximetil-butil)-3 6-dimetil-1H-pirrolo[3,2 b]piridina	396 5	
240		{5-Bromo-6-isopropil-3-[1 ((S)-2 metoxi-1 metil-etil)-3 6-dimetil-1H-p rrolo[3 2-b]piridin-5-il]-piridin-2 il}-metil-aml	445 3	

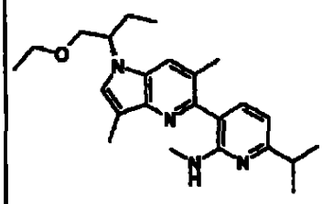
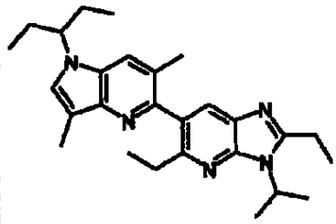
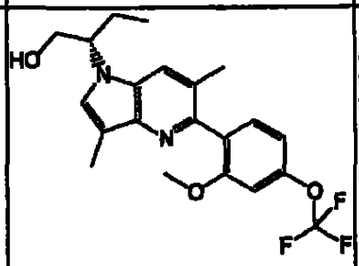
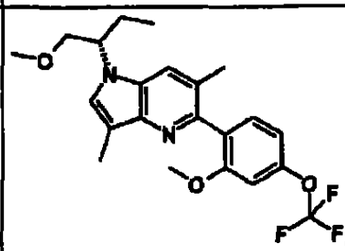
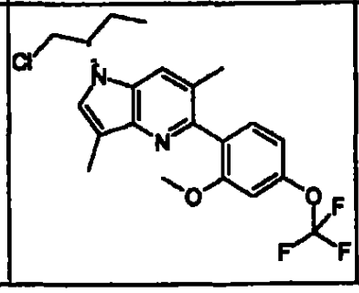
241		{5-Etil-6-isopropil-3-[1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil 1H pirrol [3 2 b]pridi -5-il] pridi 2-il}-metil-amina	395 5	
242		1-((S)-1-Fl rometil-propil)-5-(6-isopropil 2-metoxi-pridin-3-il)-3 6-dimetil-1H-pirrolo[3,2 b]piridina	370 44	1 55
243		1-((R)-1 Fluorometil-propil)-5-(6-isopropil-2-metoxi-pridin-3-il)-3 6-dimetil 1H pirrolo[3 2-b]piridina	370 5	
244		{3-[1-((S)-1 Fluorometil-propil)-3 6-dimetil-1H pirrol [3 2-b]pridin-5-il]-6-isopropil-pridin-2-il}-metil-ml	369 5	
245		(S)-3-[5-(6-isopropil 2 metoxi-pridi -3-il)-3 6-dimetil pirrolo[3 2-b]pridin-1-il]-4-metoxi butiro itnl	393 4	

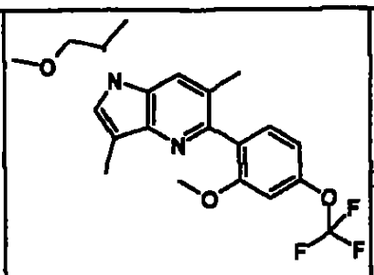
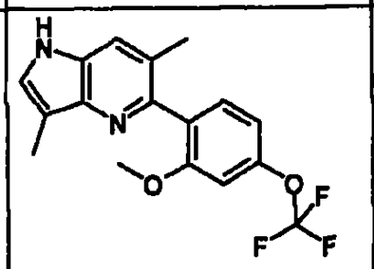
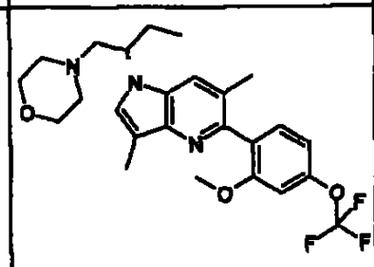
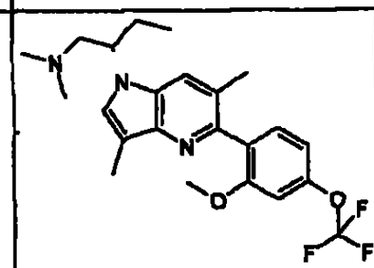
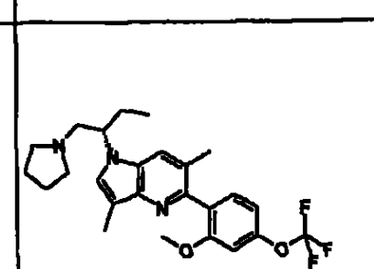
246		(R)-2-[5-(6-Isopropil-2-metoxi-piridi -3-il)-3 6-dimetil pirrolo[3 2-b]piridin-1 il]-penta 1-ol	382.5	
247		5-(6-Isopropil-2 metoxi-piridin-3-il)-1 ((R)-1 metoximetil-butil)-3 6-dimetil-1H-pirrolo[3 2-b]piridi	396.5	
248		1 ((R)-1-Fluorometil-b til)-5-(6-isopropil-2 metoxi-pirid -3-il)-3 6-dimetil 1H-pirrolo[3,2 b]piridina	384.5	
249		5-(6-Isopropil-2 metoxi-piridin-3-il)-1-(1 metoximetil-vi il)-3 6-dimetil-1H pirrol [3 2 b]piridi	366.4	
250		{6-Isopropil-3-[1 ((R)-1-metoximetil-butil)-3 6-dimetil-1H-pirrolo[3 2 b]piridin-5-il]-piridin-2-il}-metil-amina	395 6	

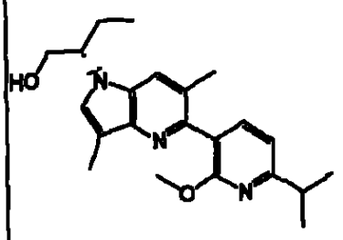
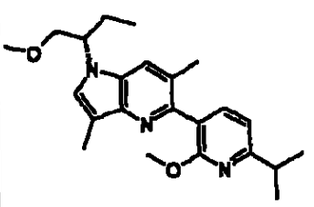
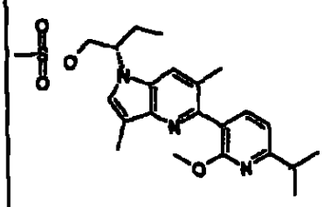
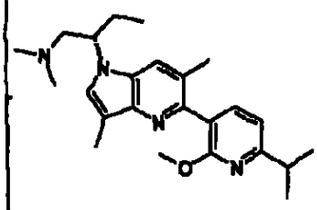
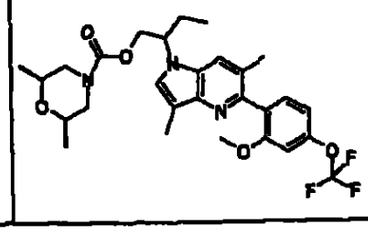
251		5-(2-Etil-6-isopropil-piridin-3-il)-1 ((R)-1 metoximetil-butil)-3 6-dimetil-1H pirrolo[3,2 b]piridi	394.4	
252		(S)-2-[6-Etil-5-(6-isopropil-2-metoxi-piridin-3-il)-3-metil-pirrolo[3,2-b]pirid 1 il]-3-metoxi-propan-1-ol	Rf 0 4(Hexo/etil Etiloacetato 1 1)	
253		6-Etil-1-((R)-1 fi rometil-2-metoxi-etil)-5-(6-isopropil-2-metoxi piridin-3-il)-3-metil-1H-pirrol [3 2 b]piridi	400.5	
254		5-(6-Isopropil 2 metoxi-p ridin-3-il)-1 (2-metoxi-1 metoximetil-etil)-3 6-dimetil-1H pirrolo[3,2 b] piridina	398 5	
255		5-(2-Etil-6-isopropil-piridin-3-il)-1-((S)-1 fi rometil-propil)-3 6-dimetil-1H pirrolo[3 2-b]piridi	368 4	

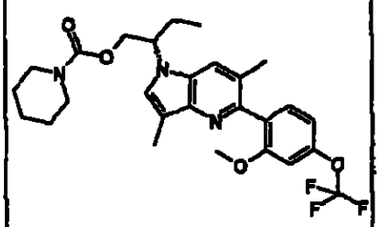
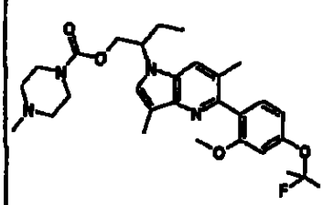
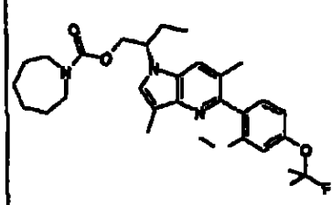
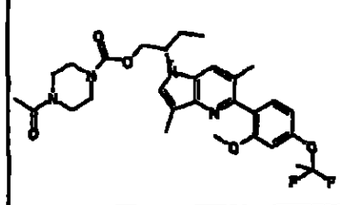
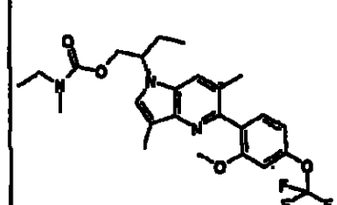
256		1 ((S)-1 Fluorometil-prop l)-5-(6-ls propil-piridin-3-il)-3 6-dimetil-1H pirrolo[3 2-b]piridl	340 4	
257		{6-Isopropil-3-[1-(2 metoxi-1 metoximetil-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridin-5-il] piridin-2 il}-metil-aml	397.5	
258		1-((S)-1-Etoximetil-propil)-5-(6-Isopropil-2-metoxi-piridl -3-il)-3 6-dimetil 1H pirrolo[3 2-b]piridl	396 5	
259		(R)-2-[5-(6-Isopropil-2-metoxi-pirid -3-il)-3 6-dimetil pirrolo[3,2-b]piridl 1 il]-3-metoxi-propan-1-ol	384 4	
260		1 ((S)-1-Fl rometil-2-metoxi-etil)-5-(6-Isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-1H-pirrolo[3 2-b]piridina	Rf 0 3 (H xa o /Etil ace tato 1 1)	

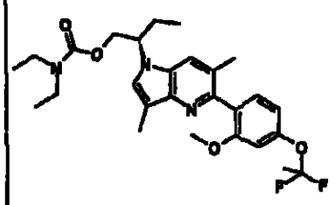
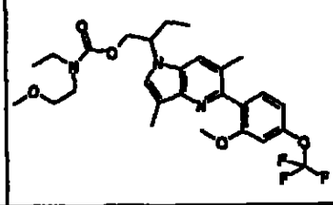
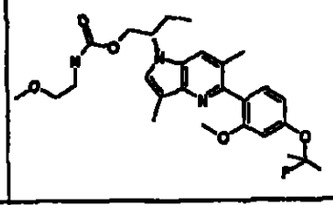
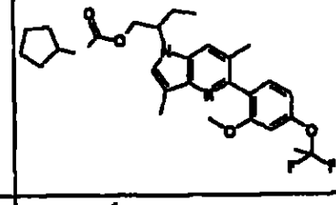
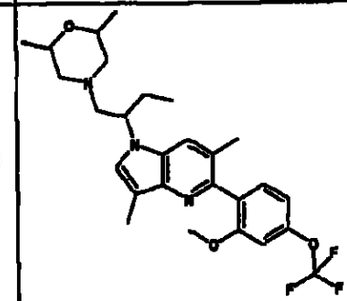
261		{3-[1-((S)-Fluorometil-2 metoxi-etil)-3 6-dimetil-1H pirrolo[3 2 b]piridin-5-il]-6-is propil-piridin-2-il}-metil-ami	Rf 0.3 (Hexano /etil Etil ace tato: 2 5/1)	
262		6-Etil-1-isopropil-5-(6-isopropil-2 metoxi-piridi -3-il)-3-metil-1H pirrolo[3 2-b]piridina	352.4	
263		[3-(6-Etil-1 isopropil-3-metil-1H pirrolo[3 2-b]piridi 5-il)-6-isopropil-piridin-2-il]-metil-mina	351 4	
264		6-Etil-5-(2-etil-6-isopropil-piridin-3-il)-1-isopropil-3-metil-1H-pirrolo[3,2 b]piridina	350.4	
265		5-(2 Etil-6-isopropil-piridin-3-il)-1-(2 metoxi-1 metoximetil-etil)-3 6-dimetil-1H pirrol [3 2-b]piridi	396.5	

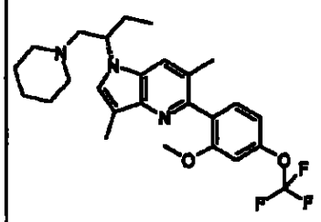
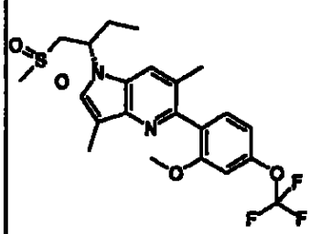
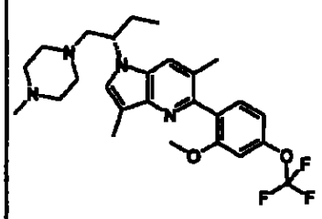
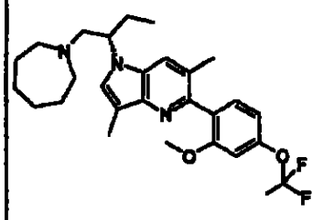
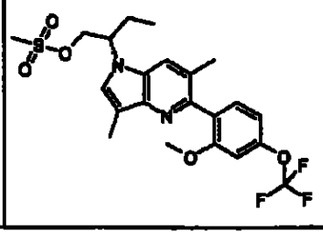
266		{3-[1-((S)-1 Etoximetil-propil)-3 6-dimetil-1H-pirrol [3 2-b]piridi 5-il]-6-isopropil-piridin-2-il}-metil-mina	395.5	
267		2 5-Dietil-6-[1-(1 etil-propil)-3 6-dimetil-1H-p rrol [3 2-b]piridi 5-il]-3-isopropil-3H imidazo[4 5-b]piridina	432.21	2.32
268		(S)-2-[5-(2-Metoxi-4-trifl rometoxi-fe il)-3 6-dimetil pirrolo[3 2 b]piridi 1-il]-b ta 1-ol	409.3	
269		1-((S)-1 Metoximetil-propil)-5-(2-metoxi-4-trifl rometoxi-fe il)-3 6-dimetil-1H-pirrol [3 2 b]piridi	423.3	
270		1-((S)-1-Cl rometil-propil)-5-(2-metoxi 4-trifluorometoxi-fe il)-3 6-dimetil-1H pirrolo[3 2-b]pi dina	427 4	

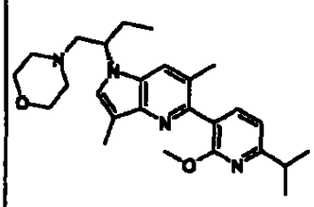
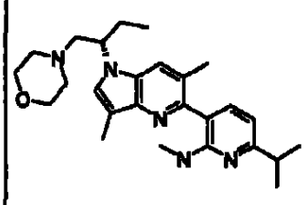
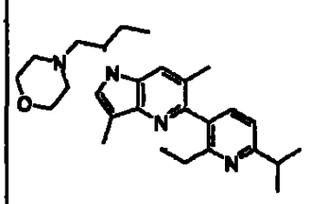
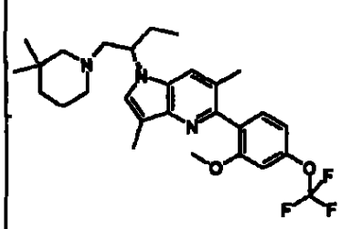
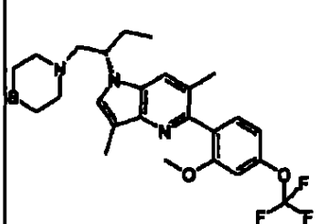
271		1-((S)-2-Metoxi-1 metil etil)-5-(2 metoxi-4- trifl orometoxi- fe il)-3 6-dimetil- 1H-pirrolo[3 2 b]piridi	409 4	
272		5-(2 Metoxi-4- trifl orometoxi- fe il)-3 6-dimetil- 1H-pirrolo[3 2 b]piridi	337 1	
273		5-(2 Metoxi-4- trifl orometoxi- fe l)-3 6-dimetil- 1-((S)-1-morfolin-4- ilmetil-propil-1H pirrolo[3,2 b]piridi	478.06	1 91
274		{(S)-2-[5-(Metoxi- 4-trifl rometoxi- fe il)-3 6-dimetil- pirrolo[3,2-b]piridi 1 1il}-butil}-dimetil- mina	436 04	1 84
275		5-(2 Metoxi-4- trifl rometoxi- fe il)-3 6-dimetil- 1 ((S)-pirrolill 1 ilmetil-propil)-1H- pirrolo[3 2-b]piridi	462.4	

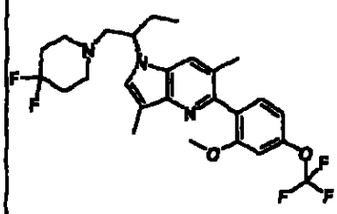
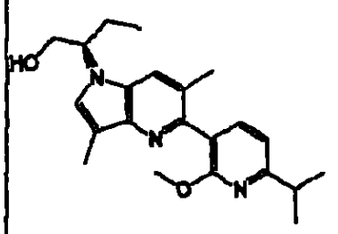
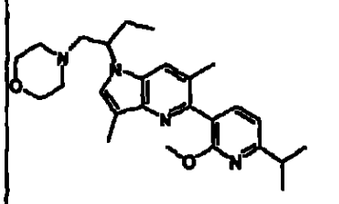
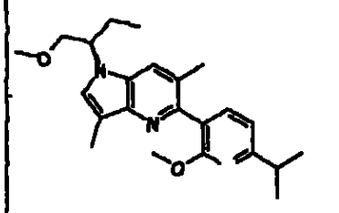
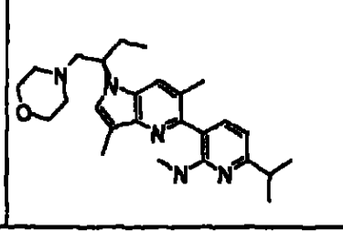
276		(S)-2-[5-(6-Isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-pirrolo[3 2-b]piridi 1 il]-butan-1-ol	368.3	
277		5-(6-Isopropil-2 metoxi-piridi -3-il)-1-((S)-1 metoximetil propil)-3 6-dimetil-1H pirrol [3 2-b]piridi	382 3	
278		Éste d Ácid metas lfónico-(S)-2-[5-(6-Isopropil-2 metoxi-piridin-3-il)-3 6-dimetil-pirrolo[3 2-b]piridin-1 il]-butilo	446 04	2 23
279		(S)-2-[5-(6-Isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-pirrolo[3 2-b]pridi 1 il]-butil]-dimetil-mi	395 13	1 87
280		Éste de 2 [5-(2 metoxi-4-trifl rometoxi-fe il)-3 6-dimetil-pirrolo[3 2 b]piridin-1 il]-butil d ácid (2R,6S)-2 6-Dimetil-m rfoli -4- 2-[5-(2-metoxi-4-carboxílico	550 1	2 31

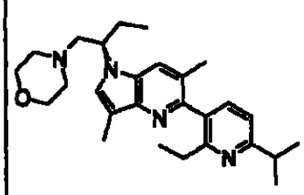
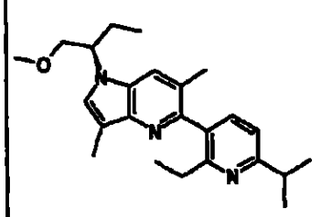
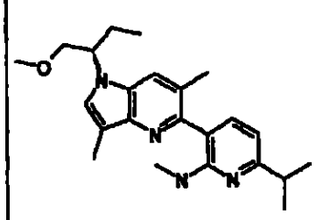
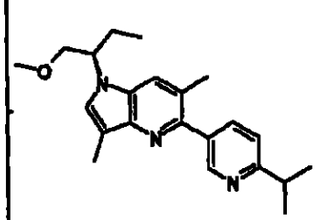
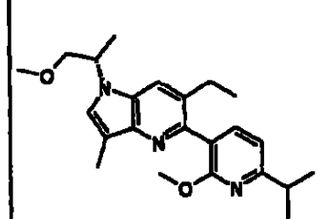
281		Éste de (S)-2-[5-(2 metoxi-4-trifl rometoxi-fe il)-3 6-dimetil-pirrolo[3 2-b]piridi 1-il]-butilo de ácid piperidin-1 carboxílico	520 11	2.36
282		Éste d (S)-2-[5-(2 metoxi-4-trifluorometoxi-fe il)-3 6-dimetil-pirrolo[3 2-b]piridi 1-il]-butilo de ácid 4-metil-piperazi 1-carbo ílico	535 13	1 25
283		Éste d (S)-2-[5-(2 metoxi-4-trifl orometoxi-fenil)-3 6-dimetil-pirrolo[3 2-b]piridin-1-il] butilo de ácido azefan-1 carboxílico	534 13	1.45
284		Éste d (S)-2-[5-(2 metoxi-4-trifluorometoxi-fe il)-3 6-dimetil-pirrol [3 2-b]piridi 1-il]-butilo de ácid 4-acetil-piperazin-1 carboxílico	563 12	1 35
285		Éste de (S)-2-[5-(2 metoxi-4-trifl rometoxi-fenil)-3 6-dimetil-pirrolo[3,2-b]piridin-1 il]-butilo d Ácid etil-metil-Carbámico	494 10	1 40

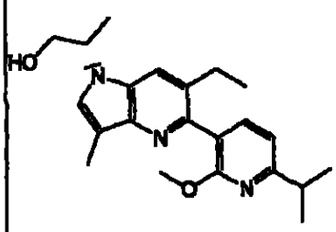
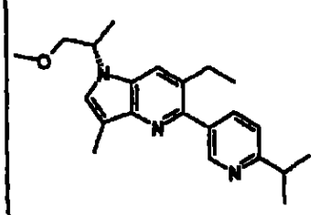
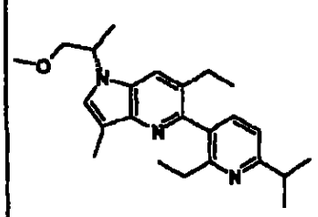
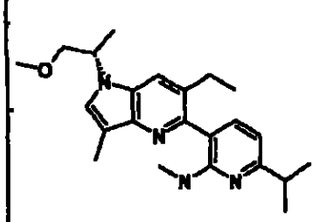
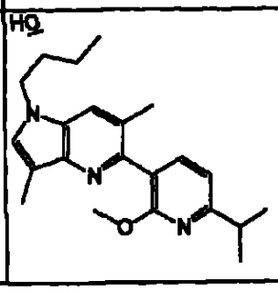
286		Éste d (S)-2-[5-(2 metoxi-4- trifl rometoxi- fenil)-3 6-dimetil- pirrolo[3,2 b]pirid 1-il]-butil d ácid dietil- carbámico	508 12	1 41
287		Éste d (S)-2-[5-(2 metoxi-4- trifl rometoxi- fe il)-3 6-dimetil- pirrolo[3 2-b]pirid 1 il]-butil d ácid etil-(2-metoxi- etil)-carbámico	538 12	1 41
288		Éste d (S)-2-[5-(2 metoxi-4- trifl rometoxi- fe il)-3 6-dimetil- pirrolo[3 2 b]pirid 1 il]-butil de ácid (2 metoxi- etil-carbámico	510 09	2 18
289		Éste d (S)-2-[5-(2 metoxi-4- trifluorometoxi- fenil)-3 6-dimetil- pirrolo[3 2-b]piridin- 1-il]-butilo d ácido ciclopentil- carbámico	520 12	1 43
290		1-[(S)-1-((2S 6R)-2 6- Dimetil morfolin-4- ilmetil)-propil]-5-(2- metoxi-4- trifluorometoxi- fe il)-3 6-dimetil- 1H-p rrolo[3 2 b] piridina	506 13	1.30

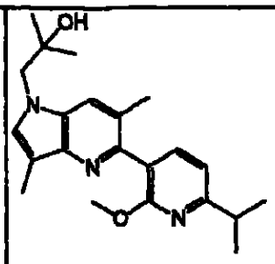
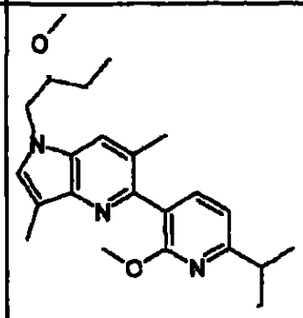
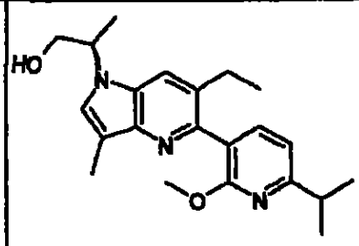
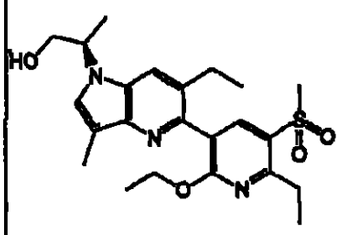
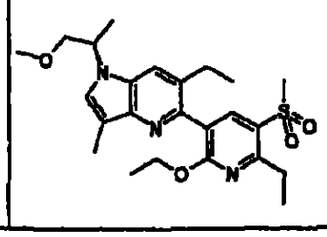
291		5-(2 Metoxi-4-trifl orometoxi-fenil)-3 6-dimetil-1-((S)-1-piperidin-1 ilmetil-propil)-1H pirrolo[3 2-b]piridi	476 13	1 85
292		1-((S)-1 Meta os ifo ilmetil propil)-5-(2-metoxi-4-trifluorometoxi fe il)-3 6-dimetil-1H-pirrolo[3 2-b]piridi	471 03	2 11
293		5-(2 Metoxi-4-trifl orometoxi-fenil)-3 6-dimetil-1 [(S)-1-(4-metil-piperazi 1-ilmetil)-propil]-1H pirrolo[3 2-b]piridi	491 13	1 84
294		1-((S)-1-Azepan-1 ilmetil-prop l)-5-(2-metoxi-4-trifluorometoxi-fenil)-3 6-dimetil-1H-pirrolo[3 2 b]piridi	490 14	1 89
295		Ésta d (S)-2 [5-(2 metoxi-4-trifluorometoxi-fenil)-3 6-dimetil-pirrol [3 2-b]piridi 1-il] butilo de ácid Meta os ifónico	487 04	2 16

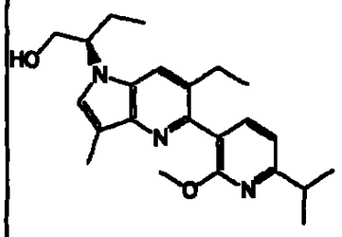
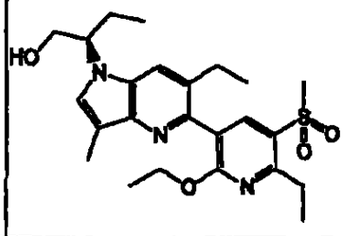
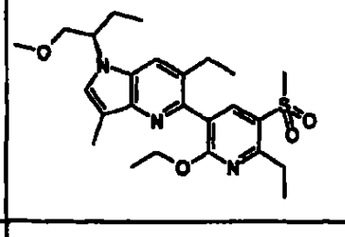
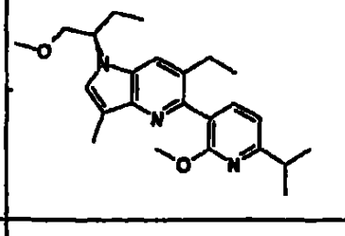
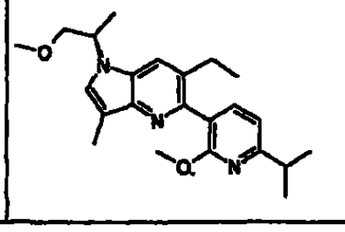
296		5-(6-Isopropil-2 metoxi-piridi -3-il)-3 6-dimetil-1-((S)-morfoli -4-ilmetil-propil)-1H pirrolo[3 2 b]piridina	437 16	2 02
297		{3-[3 6-Dimetil-1 ((S)-1 morfolin-4-ilmetil-propil)-1H pirrolo[3 2 b]piridin-5-il]-6-isopropil-piridin-2-il}-metil-amina	436 19	1 57
298		5-(2-Etil-6-isopropil-piridin-3-il)-3 6-dimetil-1-((S)-1 morfolin-4-ilmetil-propil)-1H pirrolo[3,2 b]piridi	435.20	1 57
299		1-[(S)-1-(3 3-Dimetil-piperidin-1-ilmetil)-propil]-5-(2-metoxi 4-trifluorometoxi-fe il)-3 6-dimetil-1H-pirrolo[3 2 b]pindi	504 5	
300		5-(2-Metoxi-4-trifluorometoxi fe il)-3 6-dimetil-1-((S)-1-tiomorfolin-4-ilmetil-propil)-1H pirrolo[3 2 b]piridi	494.07	1 97

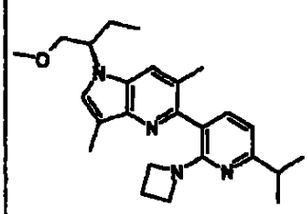
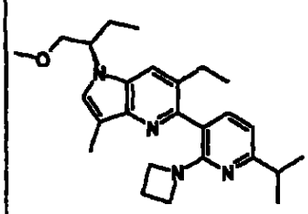
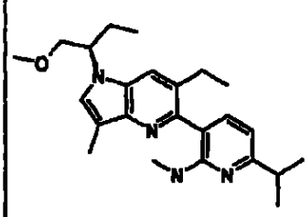
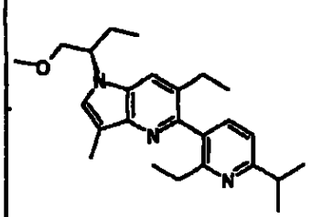
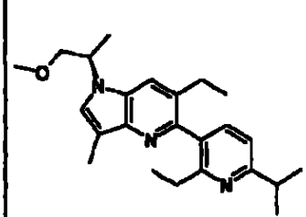
301		1 [(S)-1-(4,4-Difluoro-piperidl 1-limetil)-propil]-5-(2-metoxi 4-trifluorometoxi-fe il)-3 6-dimetil-1H pirrolo[3 2 b]piridl	512 10	2 13
302		(R)-2-{5-(6-Isopropil-2 metoxi-pirid n-3-il)-3 6-dimetil-pirrolo[3 2-b]piridin-1-il] buta 1-ol	368 16	2 21
303		5-(6-Isopropil-2 metoxi-piridin-3-il)-3 6-dimetil-1-((R)-1 m rfolin-4-limetil-propil)-1H pirrolo[3 2-b]piridl	437 16	1 95
304		5-(6-Isopropil-2 metoxi piridin-3-il)-1-((R)-1 metoximetil-prop l)-3 6-dimetil-1H pirrolo[3 2-b]piridl	382 16	2 28
305		{3-[3 6-Dimetil-1 ((R)-1-morfolin-4-limetil-propil)-1H-pirrolo[3,2 b]piridl -5-il]-6-isopropil-piridin-2 il}-metil-aml	436 16	1.58

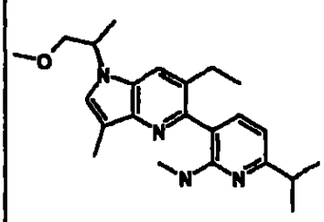
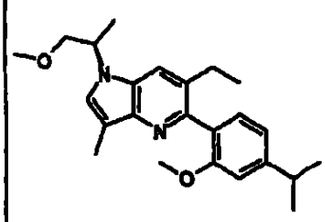
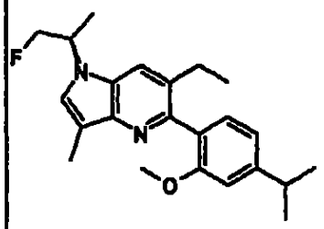
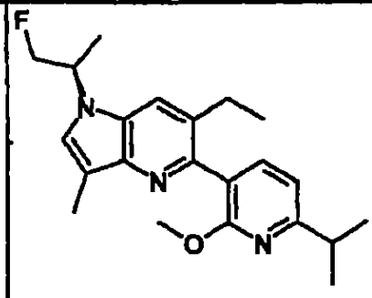
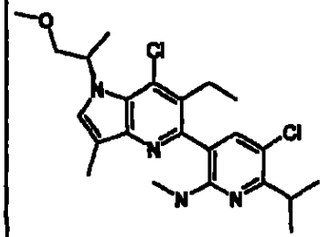
306		5-(2 Etil-6-isopropil-piridin-3-il)-3 6-dimetil-1-((R)-1 morfolil -4-ilmetil-propil)-1H pirrol [3 2-b]p ridi	435 15	1 59
307		5-(2 Etil-6-isopropil-piridin-3-il)-1-((R)-1 metoximetil-propil)-3 6-dimetil-1H pirrolo[3,2 b]piridi	380 5	
308		{6-Isopropil-3-[1-((R)-1-metoximetil-propil)-3 6-dimetil-1H-pirrol [3 2 b]piridi -5-il]-piridin-2 il}-metil-aml	381 17	1 89
309		5-(6-Isopropil-piridin-3-il-1-((R)-1 metoximetil-propil)-3 6-dimetil-1H-pirrolo[3 2 b]pind	352 4	
310		6-Etil-5-(6-isopropil-2-metoxi-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridi	382 19	2 31

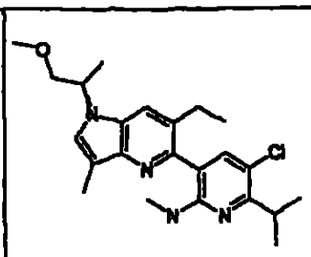
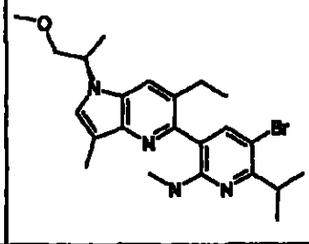
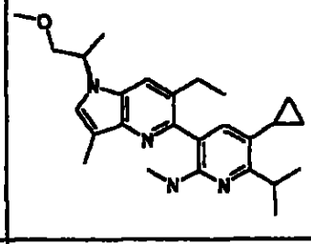
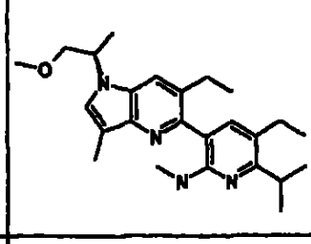
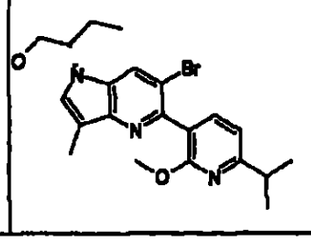
311		(S)-2-[6-Etil-5-(6 isopropil-2-metoxi-piridin-3-il)-3-metil-pirrolo[3,2 b]piridi 1 il]-propa 1-ol	368.3	
312		6-Etil-5-(6-isopropil-piridi -3-il)-1 ((S)-2 metoxi-1-metil-etil)-3-metil-1H-pirrolo[3,2 b]piridi	352 18	2 03
313		6-Etil-5-(2-etil-6-isopropil-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3-metil-1H-pirrol [3 2 b]piridi	380 20	2 08
314		(3-[6-Etil-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H pirrolo[3 2-b]piridin-5-il]-6-isopropil-piridin-2-il-metil-min	381 19	1 90
315		(R)-1-[5-(6-Isopropil-2 metoxi-piridi -3-il)-3 6-dimetil-pirrol [3 2-b]piridi 1-il]-butan-2-o-ol	368 36	2 16

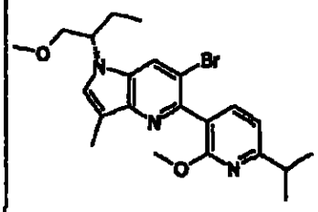
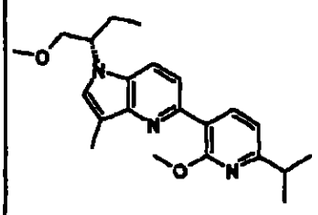
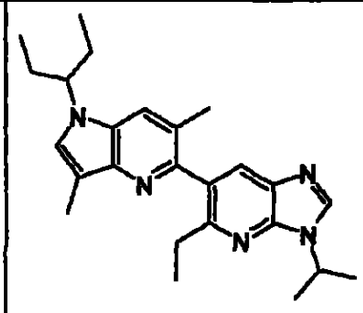
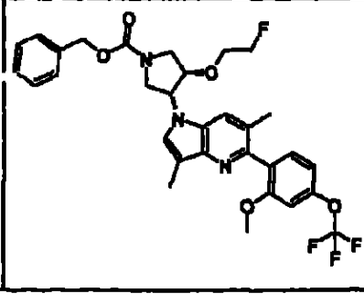
316		1-[5-(6-Isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-pirrolo[3,2-b]piridin-1 il]-2-metil-propa 2-ol	368 37	2.18
317		5-(6-Isopropil-2 metoxi-piridi -3-il)-1-((R)-2-metoxi-butil)-3 6-dimetil-1H-pirrolo[3 2 b]piridi	382 32	2 30
318		(R)-2-[6-Etil-5-(6-isopropil-2-metoxi-piridin-3-il)-3-metil-pirrolo[3 2-b]piridin-1 il]-propa 1-ol	368.4	
319		(R)-2-[5-(2 Etoxi-6-etil-5-metanos lfo il-piridin-3-il)-6-etil-3-metil-pirrolo[3 2 b]piridin-1 il]-propa 1-ol	446.35	2 04
320		5-(2 Etoxi-6-etil-5-metanos lfo il-piridin-3-il)-6-etil-1 ((R)-2-metoxi-1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridi	460 32	2 19

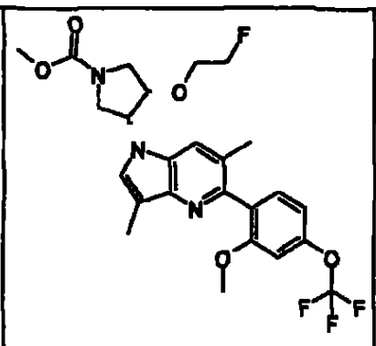
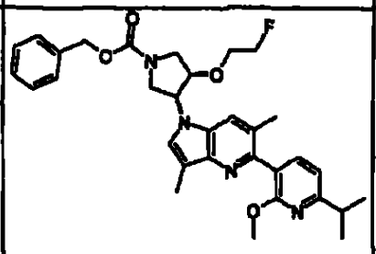
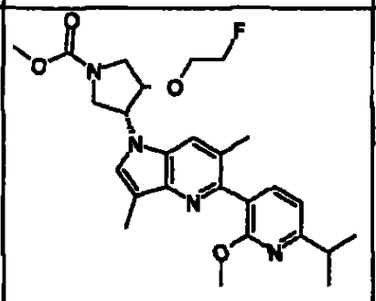
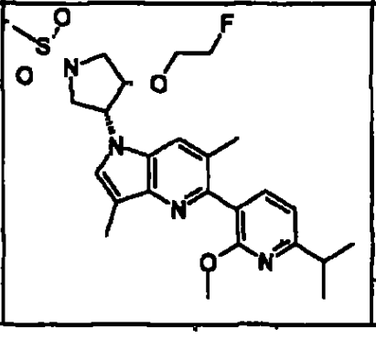
321		(R)-2-[6-Etil-5-(6-isopropil-2-metoxi-piridin-3-il)-3-metil-pirrolo[3 2-b]piridin-1-il] buta 1-ol	382.43	2.26
323		(R)-2 [5-(2 Etoxi-6-etil-5-meta os ifonil-piridin-3-il)-6-etil-3-metil-pirrolo[3 2 b]piridin-1-il]-butan-1-ol	460 16	1 37
324		5-(2 Etoxi-6-etil-5-meta os ifonil-piridin-3-il)-6-etil-1 ((R)-2 metoxdmetil-propil)-3-metil-1H pirrolo[3 2-b]pirid	474 19	1.42
325		6-Etil-5-(6-isopropil-2-metoxi-pirid 3-il)-1-((R)-1 metoxlmetil-propil)-3-metil-1H pirrol [3 2-b] pirid	396 42	2.35
326		6-Etil-5-(6-isopropil-2-metoxi-pirid -3-il)-1-((R)-2-metoxi-1-metil-etil) 3-metil-H-pirrolo[3 2 b]pirid	382 44	2 29

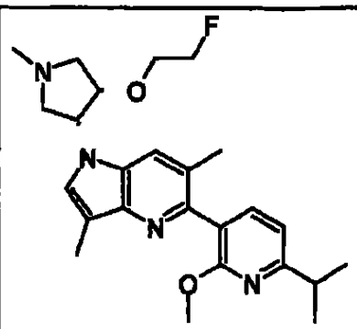
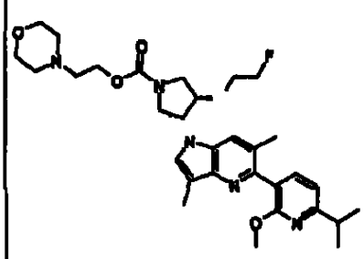
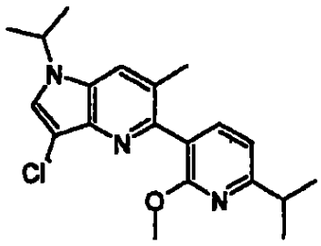
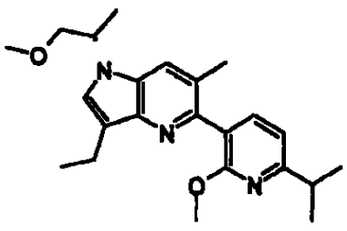
327		5-(2-Azetidin-1 il-6-isopropil-piridi 3-il)-1-((R)-1 metoximetil-propil)-3 6-dimetil-1H-pirrolo[3,2 b)piridi	407.43	2 02
328		5-(2-Azetidi 1-il-6-isopropil-piridin-3-il)-6-etil-1-((R)-1 metoximetil-propil)-3-metil-1H-pirrolo[3,2-b]piridi	421 44	2 13
329		{3-[6-Etil-1-((R)-1 metoximetil-propil)-3-metil 1H pirrol [3 2-b]piridi 5-il]-6-isopropil piridin-2-il-metil ml	395 45	1.99
330		6-Etil-5-(2-etil-6-isopropil-piridi 3-il)-1-((R)-1 metoximetil-propil)-3-metil-1H-pirrol [3 2-b]piridi	394.45	2 14
331		6-Etil-5-(2-etil-6-isopropil-piridin-3-il)-1 ((R)-2-metoxi-1 metil-etil)-3-metil-1H-pirrol [3 2 b]piridi	380 45	2 07

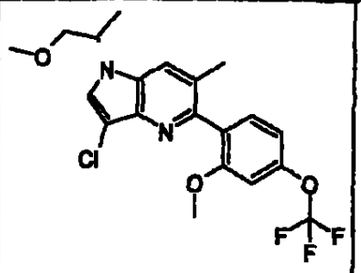
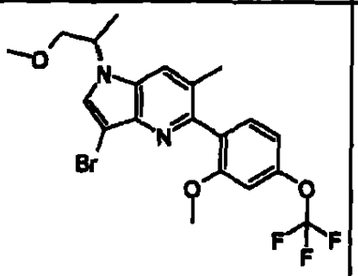
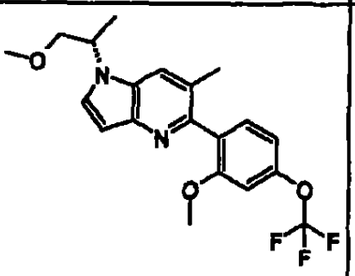
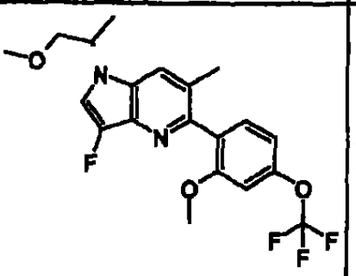
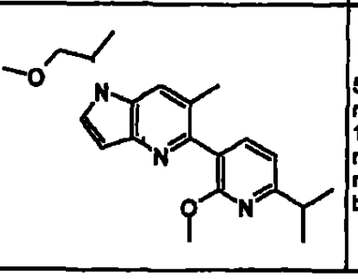
332		{3-[6-Etil-1-((R)-2-metoxi-1-metil-etil)-3-metil 1H pirrolo[3 2 b]piridi 5-il]-6-isopropil-piridin-2-il}-metil ml	381 45	1 88
333		6-Etil-5-(4-isopropil 2-metoxi-fe il)-1 ((R)-2-metoy-1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridina	381 47	2 30
334		6-Etil-1-((R)-2 fl ro-1-metil-etil)-5-(4-isopropil-2 metoxi-fenil)-3-metil-1H pirrolo[3 2 b]piridina	369 46	2 28
335		6-Etil-1-((R)-2 fl oro-1-metil-etil)-5-(6-isopropil-2 metoxi piridi 3-il)-3-metil-1H pirrol [3 2-b]piridi	370 45	2.31
336		{5-Cloro-3-[7-cl ro-6-etil-1 ((R)-2 metoxi-1-metil-etil}-3-metil 1H pirrol[3 2-b]piridin-5-il]-6-isopropil-piridin-2-il}-metil ml	449 33/ 451.33	2.91

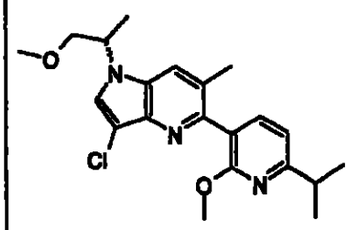
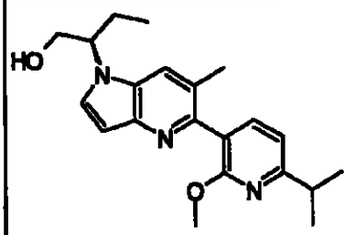
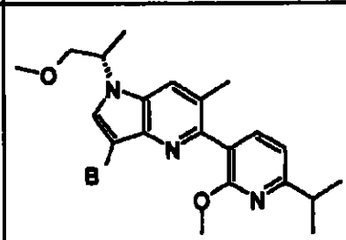
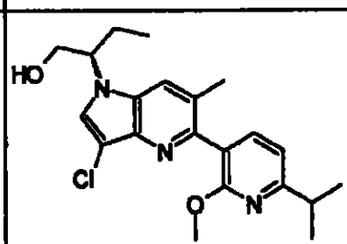
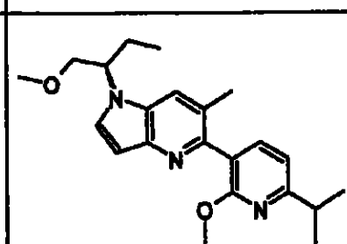
337		{5-Cloro-3-[6-etil-1 ((R)-2-metoxi 1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridi -5-il]-6-isopropil-pirid n-2 il}-metil-amina	415 40/ 417 39	2.53
338		{5-Bromo-3-[6-etil 1 ((R)-2-metoxi-1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridi -5-il]-6-isopropil-piridin-2 il}-metil-ami	459.35/ 461 35	2.55
339		{5-Cicl propil-3-[6-etil-1-{(R)-2 metoxi-1-metil-etil}-3-metil-1H pirrolo[3 2-b]piridin-5-il]-6-Is propil-piridin-2-il}-metil-mina	421 47	2.38
340		{5-Etil-3-[6-etil-1 ((R)-2-metoxi 1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridin-5-il]-6-isopropil-piridin-2 il}-metil-amina	409 49	2.29
341		(S)-2-[6-Bromo-5-(6-isopropil-2-metoxi-piridin-3-il)-3-metil-pirrolo[3 2-b]piridin-1-il]-buta 1-ol	431 35/ 433 35	2 62

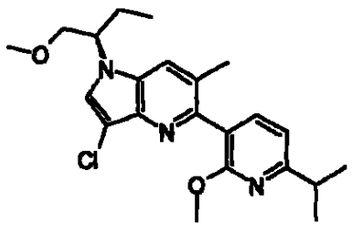
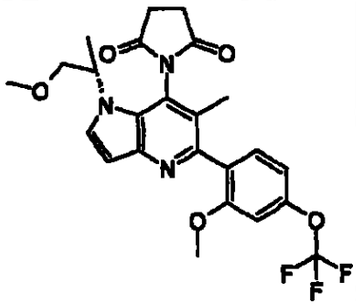
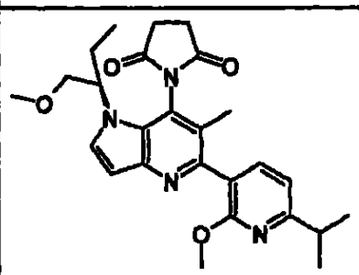
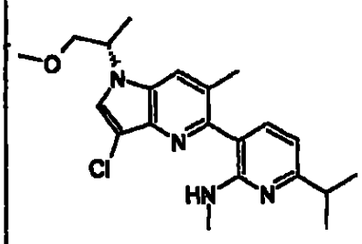
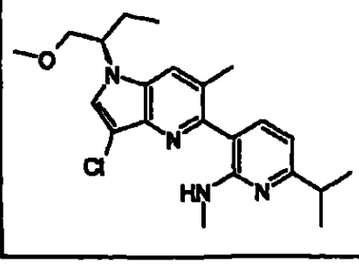
342		6-Bromo-5-(6-isopropil-2-metoxi-piridin-3-il)-1-((S)1 metoximetil-propil)-3-metil-1H-pirrolo[3 2-b]piridina	445 38/ 447 37	2 80
343		5-(6-Isopropil-2 metoxi-piridi -3-il)-1-((S)-1 metoximetil-propil)-3-metil-1H pirrolo[3 2 b]piridi	367 15	2.22
344		5-Etil-6-[1-(1-etil-propil)-3 6-dimetil-1H pirrol [3 2 b]piridi -5-il]-3-isopropil-3H-imidazo[4 5-b]piridi	404.33	1.44
345		Éste de be lio de ácid (3S 4R)-3-(2-Fl oro-etoxi)-4-[5-(2 metoxi-4-trifl rometoxi fe il) -3 6-dimetil-p rrol [3 2-b]piridi 1-il]-pirrolidi 1 carboxílico	602 06	1 47

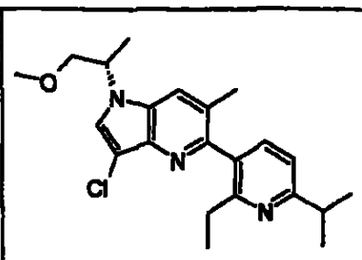
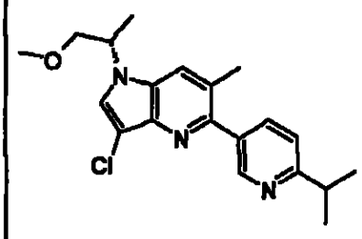
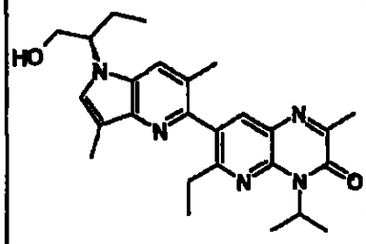
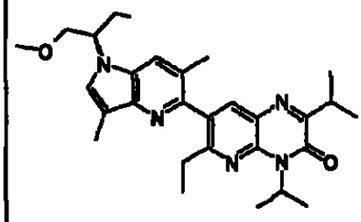
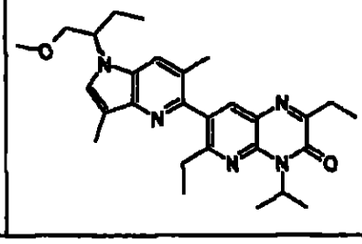
346		Éste d metilo de ácid (3S,4R)-3-(2 Fl roetoxl)-4-[5-(2 metoxl-4-trifl rometoxd-fe ll)-3 6-dimetil-pirrolo[3 2-b]piridin-1-ll]-pirrolidl 1 carboxílico	526 02	1 35
347		Éster d bencilo d ácido (3S 4R)-3-(2 Fl oroetoxl)-4-[5-(6-isopropil 2-metoxl piridl 3-ll)-3 6-dimetil-pirrolo[3 2-b]piridin-1 ll]-pirrolidin-1 carboxílico	561 11	1 49
348		Éste d metilo d ácid (3S 4R)-3-(2-Fluoroetoxl)-4-[5-(6-isopropil-2-metoxl piridl 3-ll)-3 6-dimetil-pirrolo[3 2-b]piridin-1-ll]-pirrolidin-1 carboxílico	485 13	1 39
349		1-[(3R S)-4-(2-Fluoroetoxl)-1 metanosulfonil-pirrolidin-3-ll]-5-(6-isopropil-2-metoxl-piridin-3-ll)-3 6-dimetil-1H pirrolo[3 2-b]piridl	505 10	1.35

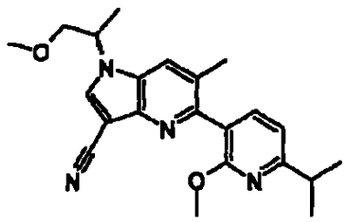
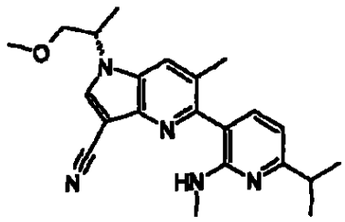
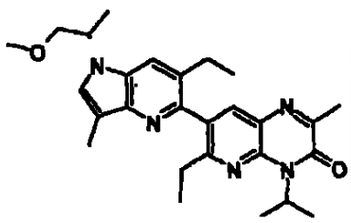
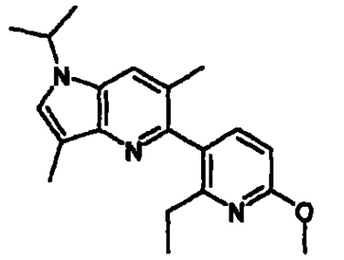
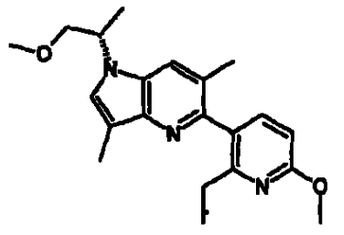
350		1-[(3R,4S)-4-(2-Fl ro-etoxi)-1-metil pirrolidin-3-il]-5-(6-isopropil-2-metoxi-piridin-3-il)-3 6-dimetil-1H pirrol [3 2-b]piridi	441 14	1 24
351		Éste 2-morfolin-4-il-etilo de ácid (3S 4R)-3-(2 Fluoro-etoxi)-4-[5-(6-I propil-2-metoxi-piridin-3-il)-3 6-dimetil-pirrolo[3 2-b]pi din-1-il]-pirrolidin-1 carboxílico	584	1.38
352		3-Cloro-1 isopropil-5-(6-isopropil-2 metoxi-piridin-3-il)-6-metil-1H pirrolo[3 2-b]piridi	358 09 360 08	1 60
353		3-Etil-5-(6-isopropil-2-metoxa-piridi -3-il)-1-((S)-2-metoxi-1 metil-etil)-6-metil 1H-pirrol [3 2 b]piridin	382 19	1.44

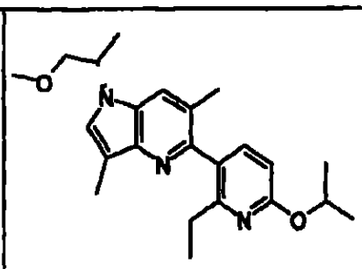
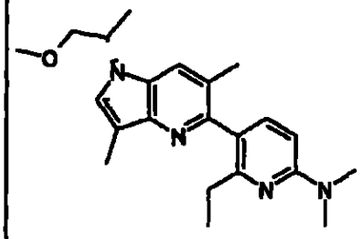
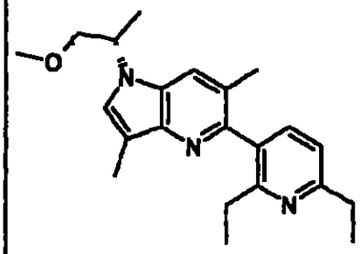
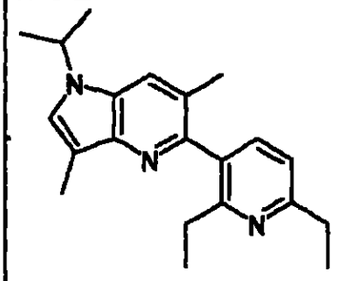
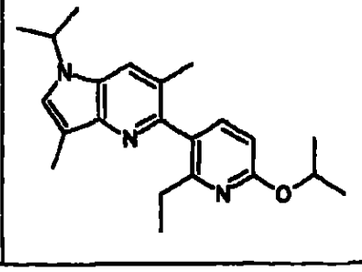
354		3-Cloro-1-(S)-2 metoxi-1-metil-etil)-5-(2-metoxi-4-trifluorometoxi-fe il)-6-metil 1H pirrolo[3 2 b]piridi	429 02 431 02	1 53
355		3-Bromo-1-(S)-2 metoxi-1-metil-etil)-5-(2-metoxi-4-trifluorometoxi fe il)-6-metil-1H pirrolo[3 2 b]piridi	472.96 474 96	1 54
356		1-((S)-2-Metoxi 1 metil-etil)-5-(2 metoxi-4-trifl orometoxi-fe il)-6-metil-1H pirrolo[3 2-b]piridi	395 04	1.34
357		3-Fluoro-1-((S)-2 metoxi-1-metil-etil)-5-(2-metoxi-4-trifluorometoxi-fe il)-6-metil 1H pirrol [3 2-b]piridi	413 02	1 49
358		5-(6-Isopropil-2 metoxi-piridin-3-il)-1 ((S)-2 metoxi-1 metil-etil)-6-metil 1H-pirrol [3 2 b]piridi	354 15	1 40

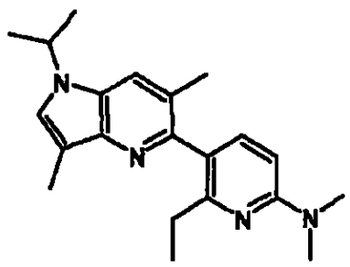
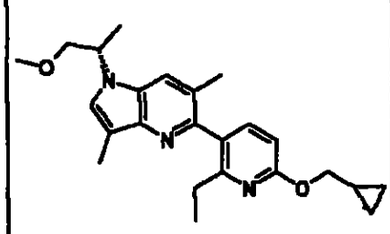
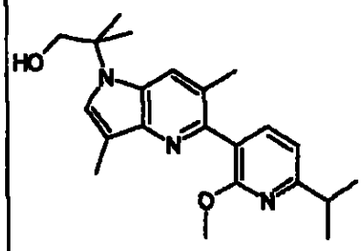
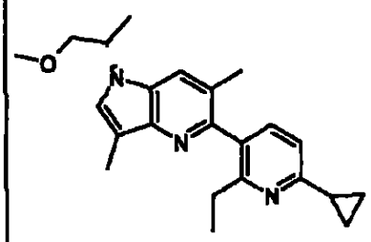
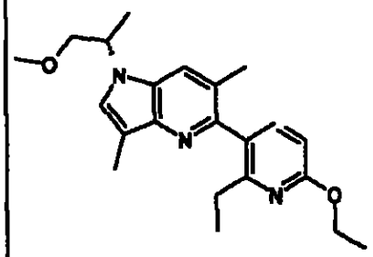
359		3-Cloro-5-(6-isopropil-2-metoxi-piridin-3-il)-1 ((S)-2 metoxi-1-metil-etil)-6-metil-1H-pirrolo[3 2-b]piridi	388 10 390 10	1 56
360		(R)-2-[5-(6-isopropil-2-metoxi-piridin-3-il)-6-metil-pirrolo[3,2 b]pi d il]-butan-1-ol	354 12	1.39
361		3-Bromo-5-(6-isopropil-2-metoxi-piridin-3-il)-1-((S)-2 metoxi-1-metil-etil)-6-metil-1H pirrolo[3 2-b]piridi	432 434	1 59
362		(R)-2-[3-Cloro-5-(6-isopropil-2-metoxi-piridin-3-il)-6-metil-pirrol [3 2-b]piridi 1-il]-butan-1-ol	388 10 390 10	1 56
363		5-(6-Isopropil-2 metoxi-piridin-3-il)-1-((R)-1 metoximetil-propil)-6-metil 1H pirrolo[3 2-b]piridina	368.26	1 44

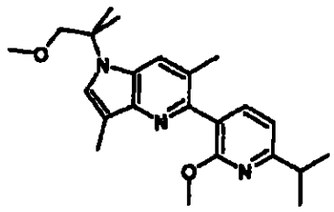
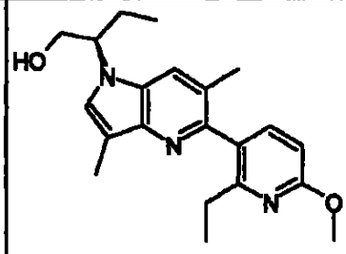
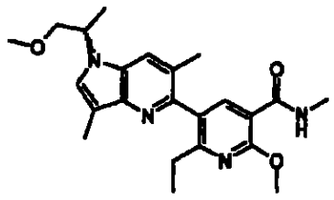
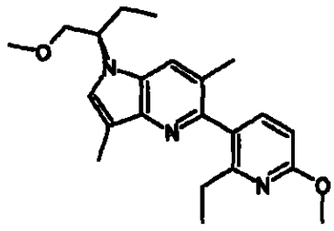
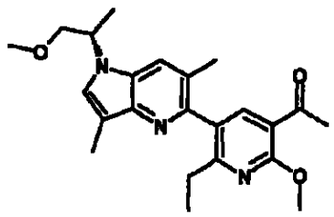
364		3-Cloro-5-(6-isopropil-2-metoxi-piridin-3-il)-1-((R)-1 metoximetil propil)-6-metil-1H-pirrolo[3 2-b]piridin	402 404	1 62
365		1-[1-((S)-2-Metoxi-1 metil-etil)-5-(2 metoxi-4-trifl orometoxi-fe il)-6-metil-1H pirrolo[3 2-b]piridin-7 il]-pirrolidin-2 5-di	492 09	1 38
366		1-[5-(6-Isopropil-2-metoxi-piridin-3-il)-1-((R)-1 metoximetil propil)-6-metil-1H pirrol [3 2-b]piridi 7-il]-pirrolidi a-2 5-diona	465 21	1 48
367		{3-[3-Cloro-1-((S)-2 metoxi-1-metil-etil)-6-metil-1H-pirrol [3 2 b]piridin-5-il]-6-isopropil-pind n-2 il}-metil-ami	387 389	1 32
368		{3-[3-Cloro-1-((R)-2 metoximetil-propil)-6-metil-1H pirrolo[3 2-b] piridin-5-il]-6-isopropil-pirid 2 il}-metil-amina	401 21 403.20	1.35

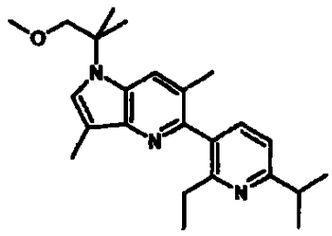
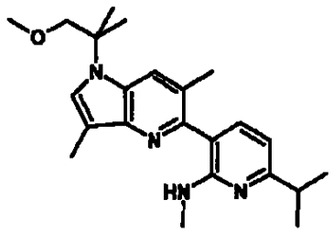
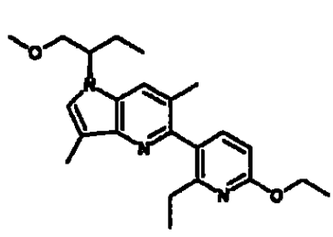
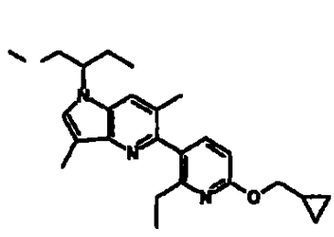
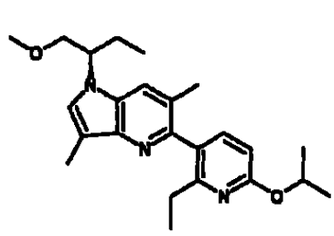
369		3-Cloro-5-(2-etil-6-isopropil-piridin-3-il)-1 ((S)-2-metoxi-1 metil-etil)-6-metil-1H pirrolo[3 2 b]piridi	386.19 388 19	1.36
370		3-Cloro-5-(6-isopropil-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-6-metil-1H-pirrolo[3 2 b]piridina	358.14 360 12	1 45
371		6-Etil-7-[1-((R)-1 hidroximetil-propil)-3 6-dimetil-1H-pirrol [3 2 b]piridi -5-il]-4-isopropil-2-metil-4H-pirido[2 3-b]pirazi -3-	448.23	1.40
372		6-Etil-2,4-diisopropil-7 [1-((R)-1 metoximetil-propil)-3 6-dimetil 1H-pirrolo[3 2 b]piridin-5-il]-4H pirido[2 3-b]pirazin-3-ona	490.31	1 53
373		2 6-Dietil-4-isopropil-7-[1-((R)-1 metoximetil-propil)-3 6-dimetil 1H-pirrolo[3 2 b]piridin-5-il]-4H pirid [2 3-b]pirazin-3-on	476.29	1 48

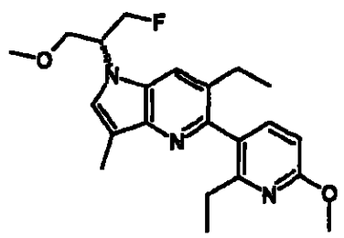
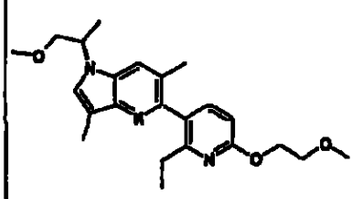
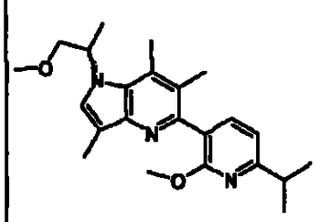
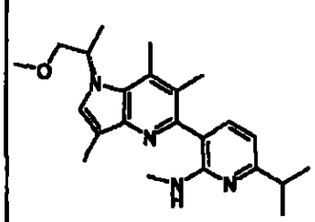
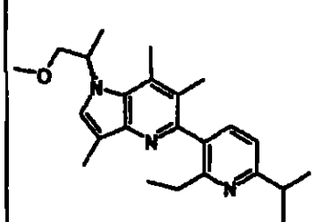
374		5-(6-isopropil-2 metoxi piridin-3-il)-1-((S)-2-metoy-1 metil-etil)-6-metil-1H-pirrolo[3 2 b]piridi a-3-carb itrilo	379 19	1 59
375		5-(6-isopropil-2 metilamino-piridin-3-il)-1-((S)-2-metoxi 1 metil-etil)-6-metil-1H-pirrolo[3 2 b]piridina-3-carbo itril	378 20	1.24
376		6-Etil-7-[6-etil-1 ((S)-2-metoxi-1 metil-etil)-3-metil-1H-pirrol [3,2 b]piridin-5-il]-4-isopropil-2 metil-4H pirido[2 3-b]pirazi -3-on	462 27	1 46
377		5-(2 Etil-6-metoxi-piridin-3-il)-1 isopropil-3 6-dimetil-1H-pirrolo[3,2 b]piridina	324 40	1 40
378		5-(2 Etil-6-metoxi-piridin-3-il)-1-((S)-2 metoxi-1-metil-etil)-3 6-dimetil-1H-pirrolo[3,2 b]piridina	354.36	1.39

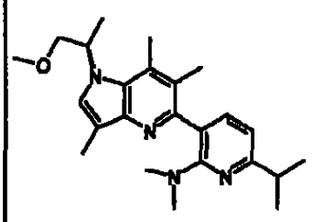
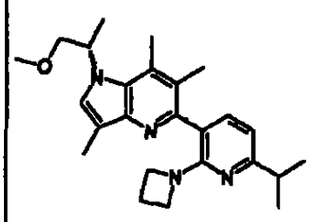
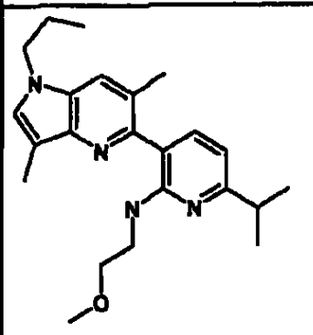
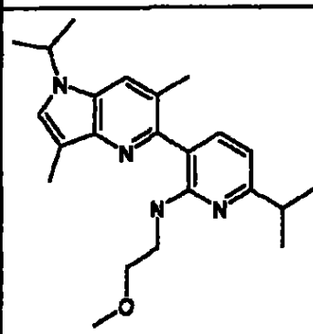
379		5-(2 Etil-6-isopropoxi-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridi	382 42	1 52
380		{6-Etil-5-[1-((S)-2 metoxi-1-metil-etil)-3 6-dimetil-1H-pirrolo[3 2 b]piridin-5-il] piridi 2-il}-dimetil-amina	367 43	1 32
381		5-(2 6-Dietil-piridi 3-il)-1-((S)-2-metoxi-1-metil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridi	352.45	1 32
382		5-(2 6-Dietil-piridin-3-il)-1-isopropil-3 6-dimetil-1H pirrolo[3 2-b]piridi	322 45	1 36
383		5-(2-Etil-6-isopropoxi-piridin-3-il)-1-isopropil-3 6-dimetil 1H pirrolo[3 2-b]piridi a-	352 45	1 54

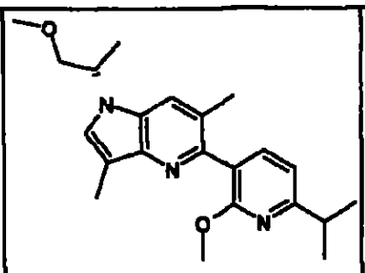
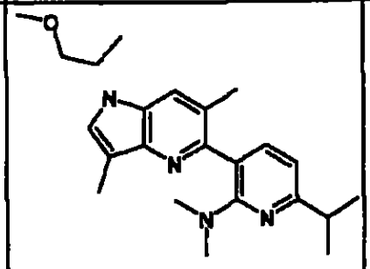
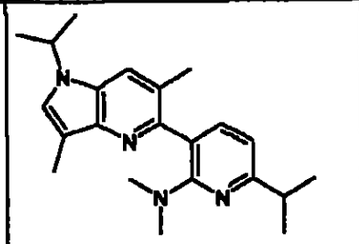
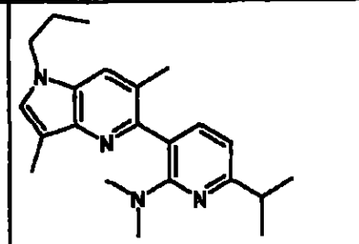
384		[6-Etil-5-(1 isopropil-3 6-dimetil-1H pirrolo[3,2 b]pridi -5-il)-pirldin-2-il]-dimetil-ami	337 44	1.31
385		5-(6-Ciclopropilmetoxi-2 etil-piridin-3-il)-1 ((S)-2-metoxi-1 Metil -etil)-3 6-dimetil-1H-pirrolo[3,2 b]piridina-	394 16	1 43
386		2 [5-(6-Isopropil-2 metoxi-pridi -3-il)-3 6-dimetil pirrolo[3,2 b]piridin-1-il]-2-metil-propa 1-ol	368 44	1 56
387		5-(6-Cl Iopropil-2 etil-piridin-3-il)-1 ((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H-pirrolo[3 2-b]piridin	364 45	1 42
388		5-(6-Etoxi-2-etil piridin-3-il)-1-((S)-2 metoxi-1-metil-etil)-3 6-dimetil-1H-pirrolo[3 2-b]pridl	368 48	1 50

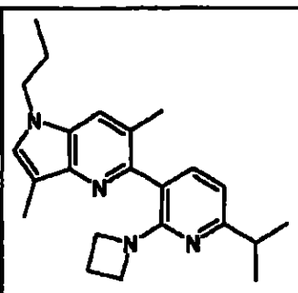
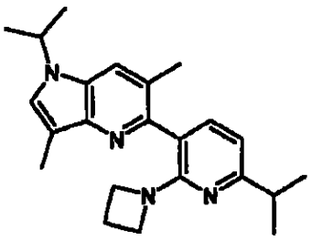
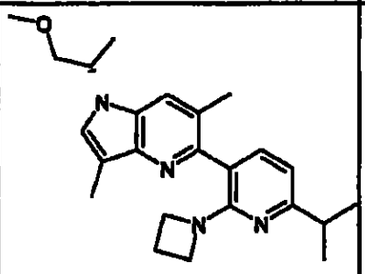
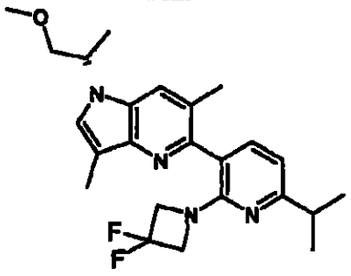
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390		(R)-2-[5-(2-Etil-6-metoxi-piridin-3-il)-3 6-dimetil-6 pirrolo[3 2-b]piridin-il]-butan-1-ol	354 46	1.49
391		6-Etil-2-metoxi-5-[1-((S)-2-metoxi-1 metil-etil)-3 6 dimetil-1H pirrol [3 2-b]piridi 5-il]-N-metil icotinamid	411.41	1.44
392		5-(2-Etil-6-metoxi-piridin-3-il)-1-((R)-1 metoximetil-propil)-3 6-dimetil-1H-pirrolo[3,2 b]piridi	368 47	1 50
393		1-[6-Etil-2-metoxi 5-[1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridin-5-il]-piridin-3-il}-eta	396 43	1.43

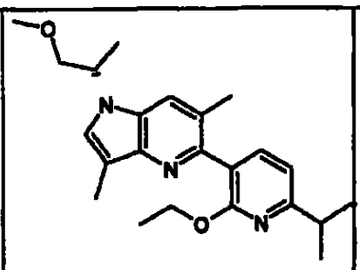
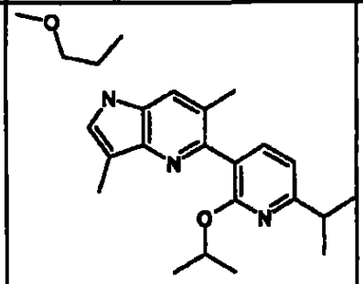
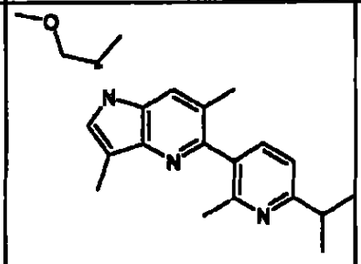
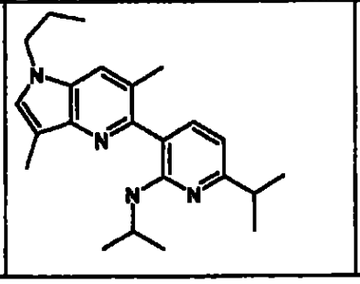
394		5-(2 Etil-6-isopropil-piridin-3-il)-1-(2-metoxi-1 1-dimetil-etil)-3 6-dimetil 1H-pirrol [3 2 b]piridi	380 49	1 41
395		(6-isopropil-3-[1-(2 metoxi-1 1-dimetil-etil)-3 6-dimetil-1H pirrolo[3 2 b]piridi 5-il]-piridi 2 il)-metil-amina	381 49	1.37
396		5-(6-Etoxi-2-etil piridin-3-il)-1 ((R)-1 metoximetil-propil)-3 6-dimetil-1H-pirrol [3 2 b]piridi	382 48	1 49
397		5-(6-Ciclopropilmetoxi-2 etil-piridin-3-il)-1 ((R)-1-metoximetil-propil)-3 6-dimetil-1H-pirrolo[3 2 b]piridi	408 46	1.56
398		5-(2-Etil-6-isopropoxi-piridi -3-il)-1-((R)-1-metoximetil-propil)-3 6-dimetil 1H-pirrol [3 2-b]piridi	396.51	1 54

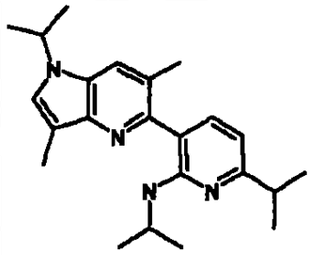
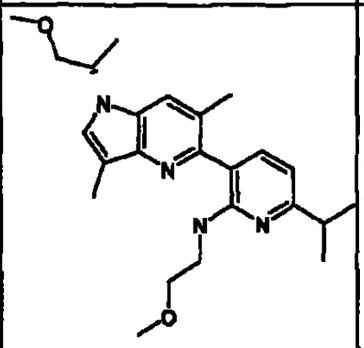
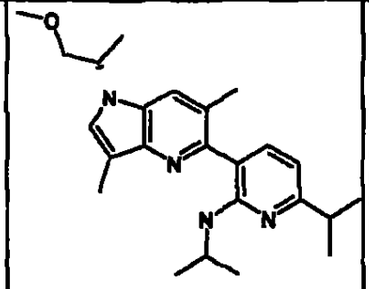
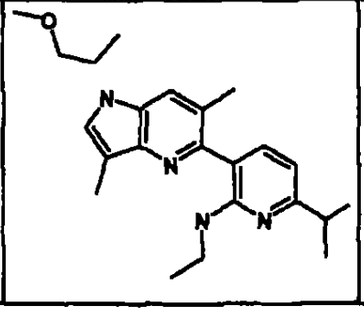
399		6-Etil-5-(2-etil-6-metoxi-piridin-3-il)-1 ((R)-2-fluoro-1 metoximetil-etil)-3-metil-1H-pirrolo[3,2-b]piridi	386 44	1 44
400		5-[2 Etil-6-(2-metoxi-etoxi)-piridi -3-il] 1-((S)-2 metoxi-1-metil-etil)-3 6-dimetil-1H-pirrolo[3 2 b]piridi	398 34	1 41
401		5-(6-Isopropil-2 metoxi-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3 6 7 trimetil-1H pirrol [3 2-b]piridi	382 3	
402		{6-Isopropil-3-[1-((S)-2 metoxi-1 metil-etil)-3 6 7 trimetil-1H-pirrolo[3 2 b]piridin-5-il]-piridi 2-il}-metil-amina	381 2	
403		5-(2 Etil-6-isopropil-piridin-3-il)-1-((S)-2 metoxi-1-metil etil)-3 6 7-trimetil-1H pirrolo[3,2-b]pirid na	380.2	

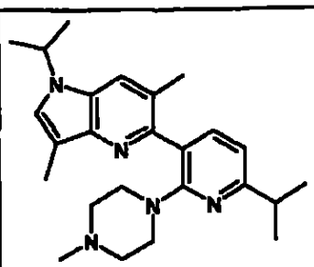
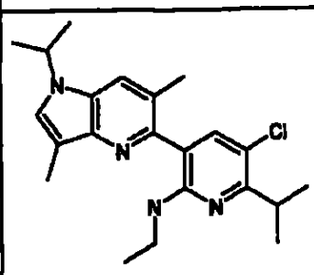
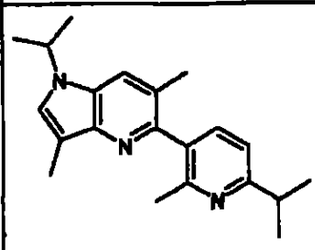
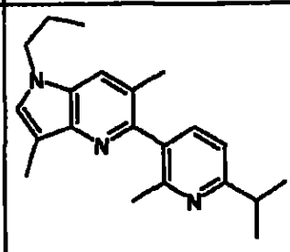
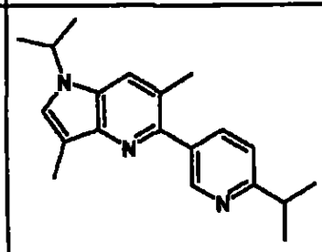
404		(6-Isopropil-3-[1-((S)-2 metoxi-1 metil-etil)-3 6 7-trimetil-1H-pirrolo[3 2 b]piridin-5-il] piridi 2-il)-dimetil-ami	395.3	
405		5-(2-Azetidi 1-il-6-isopropil-piridin-3-il)-1 ((S)-2-metoxi-1 metil-etil)-3 6 7 trimetil-1H pirrolo[3 2 b]piridina	407 6	
406		[3-(3 6-Dimetil-1 propil-1H-pirrolo[3 2 b]piridi -5-il)-6-isopropil-piridin-2-il]-(2-metoxi-etil)-mi	381.3	1 95
407		6-Isopropil-3-(1 isopropil-3 6-dimetil-1H-pirrolo[3 2 b]piridin-5-il)-piridi 2-il]-(2-metoxi-etil)-amina	381 3	1 88

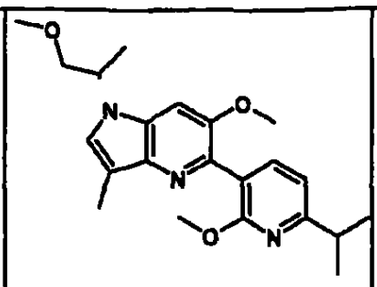
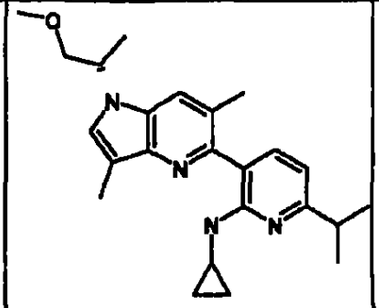
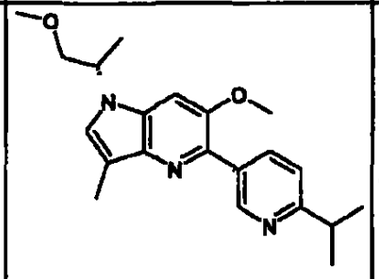
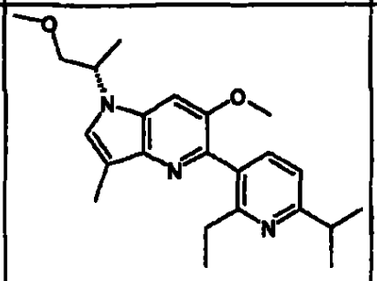
408		5-(6-Isopropil-2 metoxi-piridin-3-il)-1 ((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3,2-b]piridina	368.2	2.28
409		{6-Isopropil-3-[1-((S)-2-metoxi-1-metil-etil)-3 6-dimetil-1H-pirrol [3 2-b]piridin-5-il]-piridin-2-il}-dimetil-ami	381.3	2 00
410		[6-Isopropil-3-(1 isopropil-3 6-dimetil 1H-pirrolo[3 2 b]piridin-5-il)-piridi 2-il]-dimetil-ami	351 4	2 07
411		[3-(3 6-Dimetil-1 propil-1H-pirrol [3,2 b]piridin-5-il)-6-isopropil piridin-2-il]-dimetil-amina	351.4	2 12

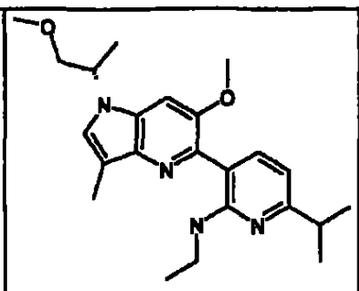
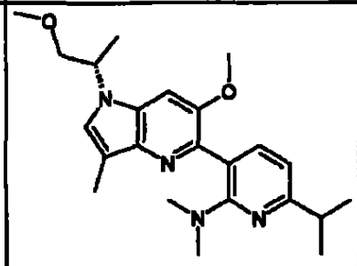
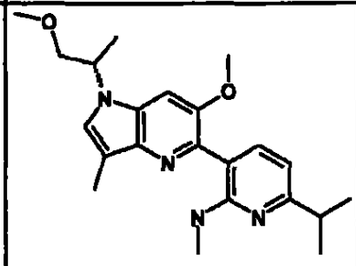
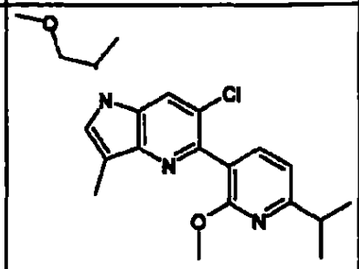
412		5-(2-Azetidin-1-il-6-isopropil-piridin-3-il)-3 6-dimetil 1-propil-1H pirrolo[3 2 b]piridi	363 4	1 87
413		5-(2-Azetidin-1 il-6-isopropil-piridin-3-il)-1 isopropil-3 6-dimetil-1H pirrol [3 2-b]piridi	363 4	1 82
414		5-(2-Azetidin-1 il-6-is propil-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrol [3 2-b]p ridi	393 4	1 75
415		5-[2-(3 3-Difl ro-azetidin-1-il)-6-isopropil-piridin-3-il] 1 ((S)-2 metoxi-1 metil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridi	429.2	2.38

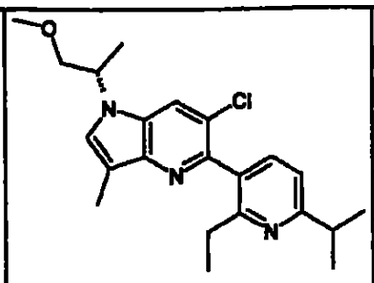
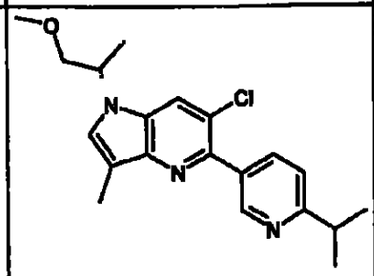
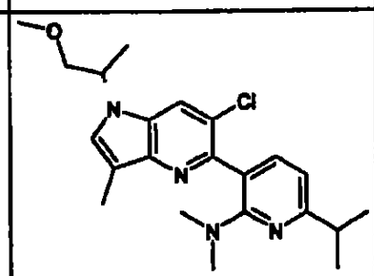
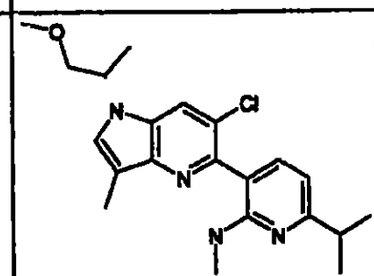
416		5-(2 Etoxi-6-isopropil-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3 2 b]piridina	382 1	2 52
417		5-(2 isopropoxi-6-isopropil-piridin-3-il)-1 ((S)-2 metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3,2-b]piridi	396.2	2.57
418		5-(6-isopropil-2 metil-piridin-3-il)-1 ((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H-pirrol [3 2-b]piridin	352 1	1 60
419		[3-(3 6-Dimetil-1 propil-1H-pirrolo[3,2 b]piridin-5-il)-6-isopropil-piridin-2-il]-isopropil-amina	365.2	2 13

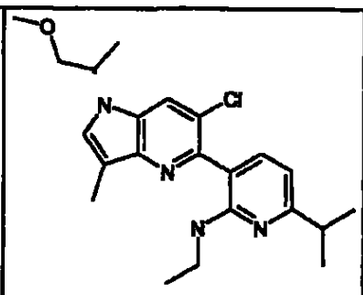
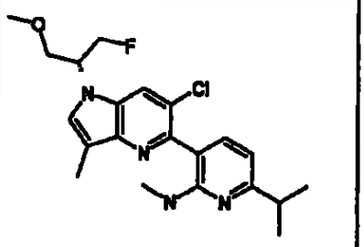
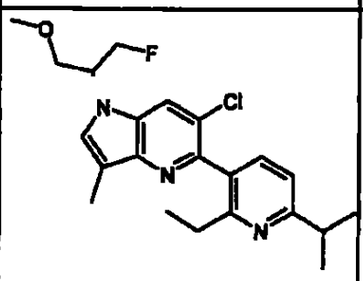
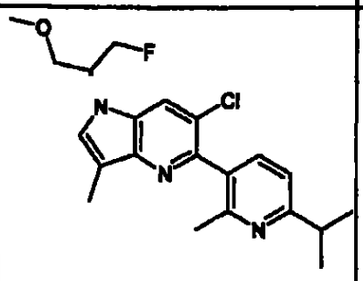
420		Isopropil-[6-isopropil-3-(1-isopropil-3 6-dimetil-1H-pirrolo[3 2-b]piridin-5-il)-piridi -2 il]-mi	365 2	2 1
421		{6-Isopropil-3-[1-(2 metoxi-1-metil-etil)-3 6-dimetil 1H-pirrolo[3 2-b]piridin-5-il] piridi -2-il}-(2 metoxi-etil)-ami	411.2	1 83
422		Isopropil-(6-isopropil-3-[1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridin-5-il]-piridin-2-il)-ami	395.2	2 02
423		Etil-(6-isopropil-3-[1-((S)-2-metoxi-1 metil-etil)-3 6-dimetil-1H pirrolo[3,2 b]piridin-5-il]-piridi -2-il)-ami	381 2	1 77

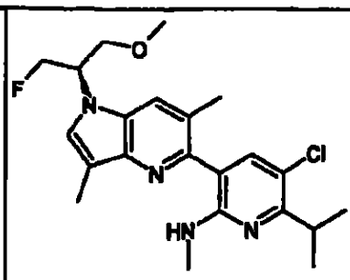
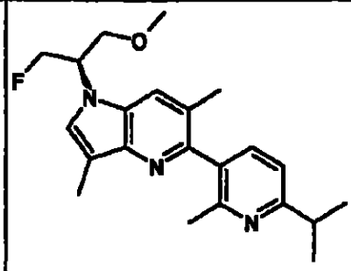
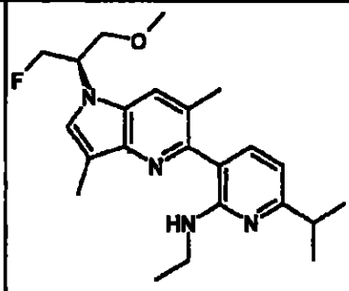
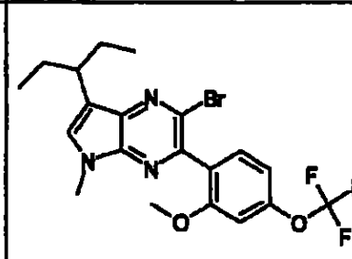
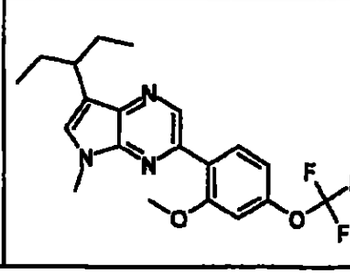
424		1 Isopropil-5-[6-isopropil-2-(4-metil-piperazi 1-il)-piridin-3-il]-3 6-dimetil 1H pirrol [3 2-b]piridi	406.3	1 67
425		[5-Cloro-6-isopropil-3-(1 isopropil-3 6-dimetil-1H pirrolo[3,2-b]piridin-5-il)-piridin-2 il]-etil-amina	385.2	2 78
426		1 Isopropil-5-(6-isopropil-2-metil-piridin-3-il)-3 6-dimetil-1H pirrolo[3,2-b]piridi	322.2	1 68
427		5-(6-Isopropil-2 metil-piridin-3-il)-3 6-dimetil-1 propil-1H-pirrolo[3 2 b]piridi	322.2	1 72
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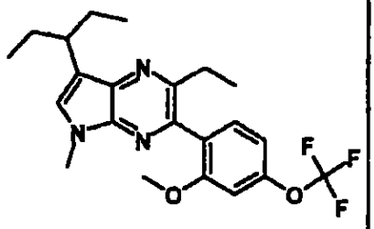
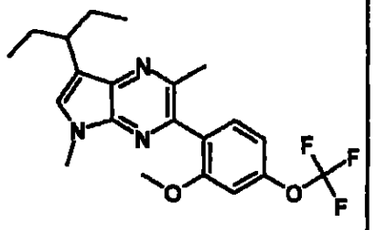
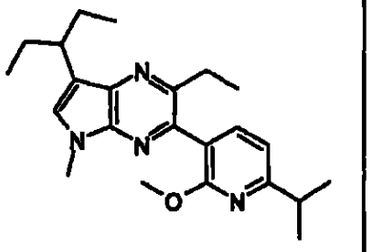
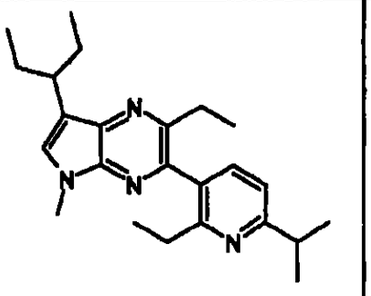
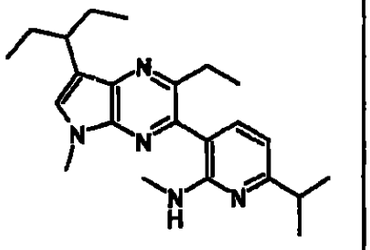
429		5-(6-Isopropil-2 metoxi-piridi -3-il)-6-metoxi 1-((S)-2-metoxi-1 metil-etil)-3-metil-1H-pirrolo[3 2-b]piridi	384 2	2 40
430		Ciclopropil-{6-isopropil-3-[1-((S)-2 metoxi-1-metil-etil)-3 6-dimetil-1H-pirrolo[3,2 b]piridi -5-il]-piridin-2 il}-amina	393 3	1 7
431		5-(6-Isopropil-piridin-3-il)-6-metoxi-1 ((S)-2-metoxi-1-metil-etil)-3-metil-1H pirrolo[3 2-b]piridi	354.2	2 02
432		5-(2 Etil-6-isopropil-piridin-3-il)-6-metoxi-1-((S)-2 metoxi-1 metil-etil)-3-metil-1H pirrolo[3 2-b]piridi	382.3	1 94

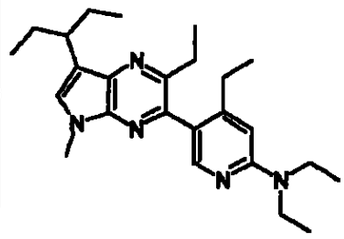
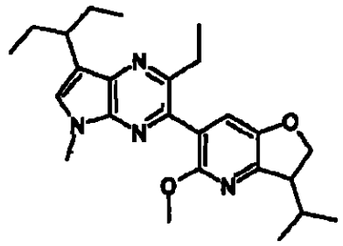
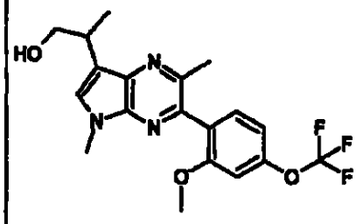
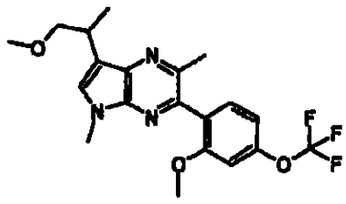
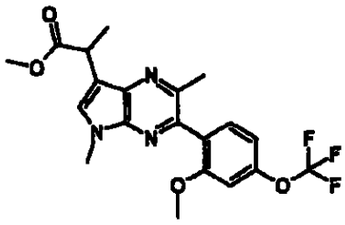
433		Etil-(6-isopropil-3-[6-metoxi-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H-pirrol [3 2-b]piridi 5-il]-piridi -2-il}-ami	397.3	2 14
434		{6-isopropil-3-[6-metoxi-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H-pirrol [3 2-b]piridin-5-il]-piridi -2-il}-dimetil-ami	397.2	1 97
435		{6-isopropil-3-[6-metoxi-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H-pirrolo[3 2-b]piridin-5-il]-piridi -2-il}-metil-ami	383 3	1 93
436		6-Cloro-5-(6-isopropil-2-metoxi-piridin-3-il)-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H-pirrolo[3,2-b]piridi	388 2	3 15

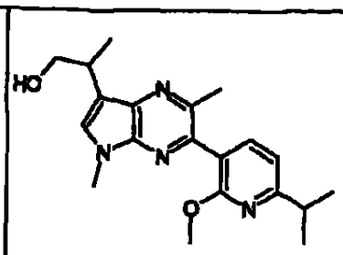
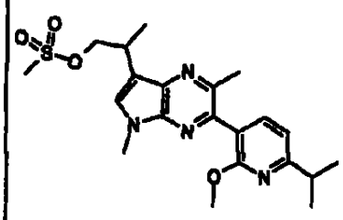
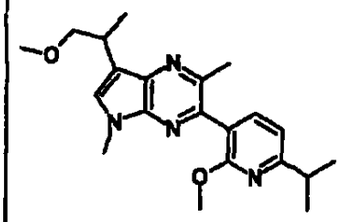
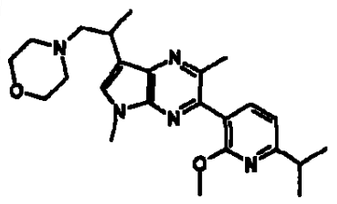
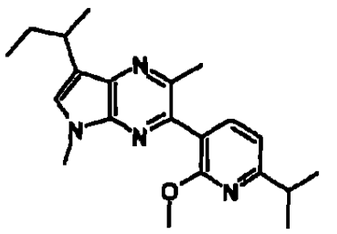
437		6-Cloro-5-(2-etil-6-isopropil-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridi	386.2	2 02
438		6-Cl ro-5-(6-isopropil-piridin-3-il)-1-((S)-2-metoxi-1 metil-etil)-3-metil-1H-pirrolo[3 2 b]piridi	358.2	2 15
439		{3-[6-Cl ro-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H pirrolo[3,2 b]piridin-5-il]-6-isopropil-piridin-2-il}-dimetil ml	401.2	2 12
440		{3-[6-Cloro-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H pirrolo[3,2 b]piridin-5-il]-6-isopropil-piridi -2-il}-metil-aml	387.2	2 09

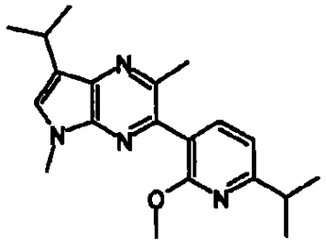
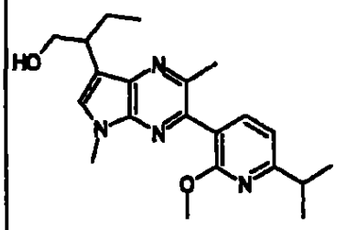
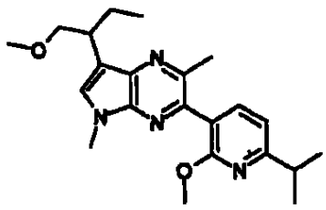
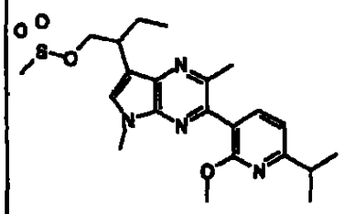
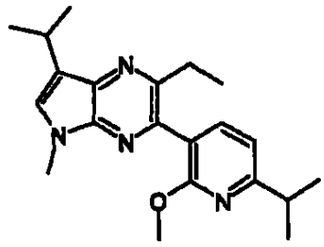
441		{3-[6-Cloro-1-((S)-2 metoxi-1-metil-etil)-3-metil-1H pirrolo[3,2-b]piridin-5-il]-6-isopropil-piridin-2-il-etil-mina	401 2	2.22
442		{3-[6-Cloro-1-((R)-1 fl orometil-2-metoxi-etil)-3-metil-1H-pirrol [3,2 b]piridin-5-il]-6-isopropil-piridin-2 il)-metil-ami	405 2	2 09
443		6-Cloro-5-(2-etil-6-isopropil-piridin-3-il)-1 ((R)-1-fl rometil-2 metoxi-etil)-3-metil-1H-pirrol [3 2 b]piridi	448 12	2 34
444		6-Cloro-1-((R)-1 fluoro-metil-2 metoxi-etil)-5-(6-is propil-2-metil-piridin-3-il)-3-metil-1H-pirrolo[3,2 b]piridi	390 11	2 17

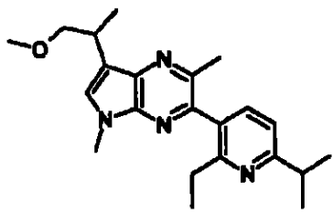
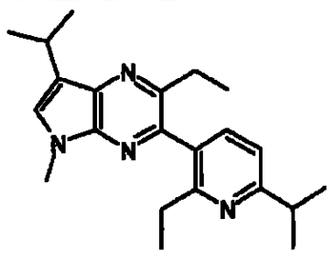
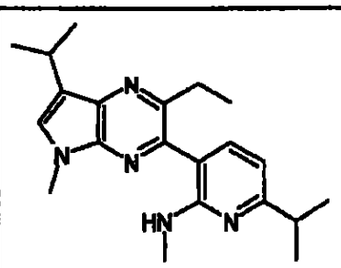
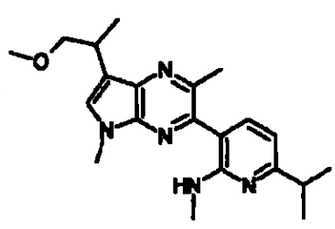
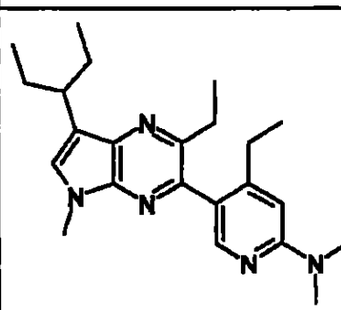
445		(5-Cl ro-3-[1-((R)-1 fl orometil-2-metoxi-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridi 5-il]-6-isopropil-piridin-2-il}-metil-ml	419 2	2 67
446		1 (R)-1-Fl orometil-2 metoxi-etil)-5-(6-isopropil-2-metil-piridin-3-il)-3 6-dimetil-1H pirrolo[3,2-b]piridi	370.20	1 83
447		Etil-(3-[1-((R)-1 fl orometil-2 metoxi-etil)-3 6-dimetil-1H pirrolo[3 2-b]piridin-5-il]-6-isopropil-piridin-2-il}-ami	399.20	2 03
448		2-Bromo-7-(1-etil-propil)-3-(2 metoxi 4-trifl rometoxi-fe il)-5-metil-5H pirrolo[2 3-b]pirazi	472.30	
449		7 (1 Etil-propil)-3-(2-metoxi-4-trifl rometoxi-fe il)-5-metil-5H-pirrolo[2 3-b]pirazina	394 3	

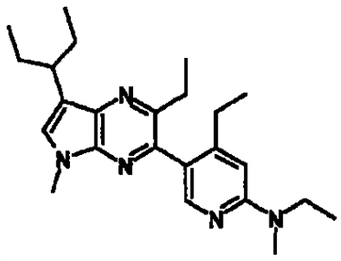
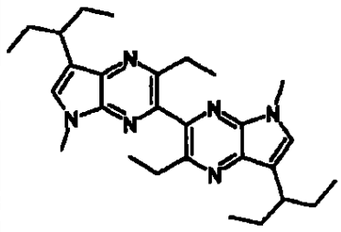
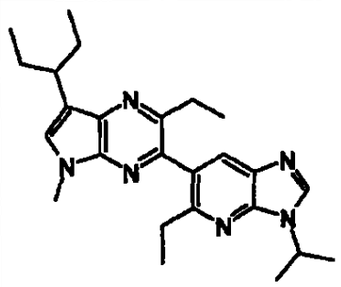
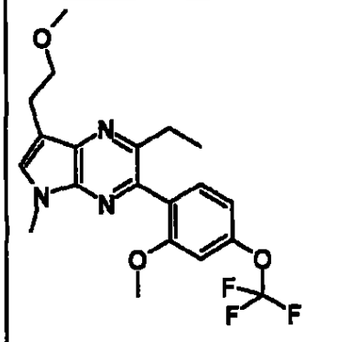
450		2-Etil 7-(1-etil-propil)-3-(2-metoxi-4-trifluorometoxi-fe il)-5-metil-5H pirrolo[2 3-b]pira ina	422.5	
451		7-(1 Etil-propil)-3-(2-metoxi-4-trifl rometoxi-fenil)-2 5-dimetil-5H-pirrolo[2 3-b]pirazina	408 5	
452		2-Etil-7-(1-etil-propil)-3-(6-isopropil 2-metoxi-piridi -3-il)-5-metil-5H pirrolo[2 3-b]pirazina	381.2	
453		2 Etil-3-(2-etil-6-isopropil-piridin-3-il)-7-(1-etil-propil)-5-metil-5H-pirrol [2 3-b]pirazina	379 4	
454		(3-[2 Etil-7-(1-etil-propil)-5-metil-5H-pirrolo[2 3-b]pira in-3-il]-6-isopropil-piridin-2 il-metil-mina	380.5	

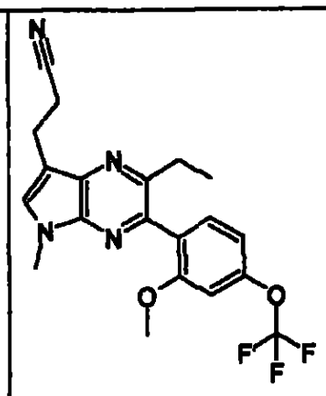
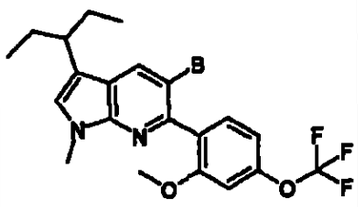
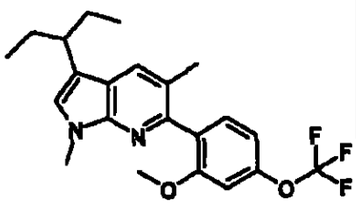
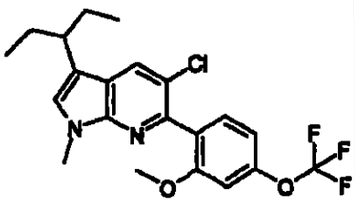
455		Dietil-[4-etil-5-[2 etil-7-(1-etil-propil)-5-metil-5H-pirrolo[2 3-b]pira in-3-il]-piridin-2-il]-mi	408 37	1 54
456		2 Etil-7-(1-etil-propil)-3-(3-isopropil-5-metoxi-2 3-dihidro-furo[3 2 b]piridin-6-il)-5-metil-5H pirrolo[2 3-b]pirazina	423 14	1 92
457		2-[3-(2 Metoxi-4-trifl rometoxi-fe il)-2 5-dimetil-5H-pirrolo[2 3-b]pirazi 7-il]-propan-1-ol	396 05	1 70
458		7-(2-Metoxi-1 metil-etil)-3-(2 metoxi-4-trifl orometoxi-fenil)-2 5-dimetil-5H-pirrolo[2 3-b]pirazina	410 03	1 77
459		Éste d metilo de ácid 2-[3-(2-Metoxi-4-trifl rometoxi-fe il)-2 5-dimetil-5H pirrol [2 3-b]pirazi 7-il]-propionico	424 00	1 74

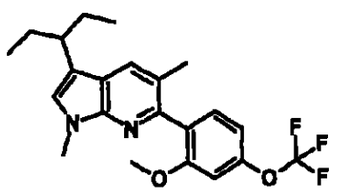
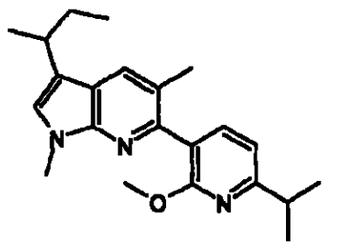
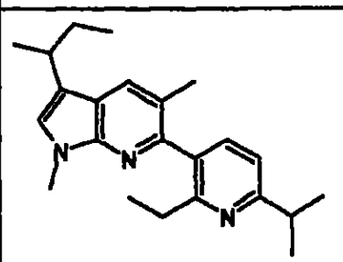
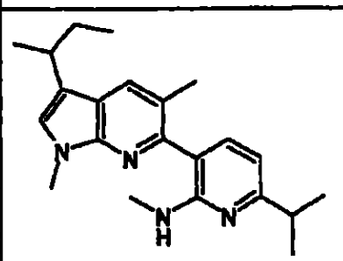
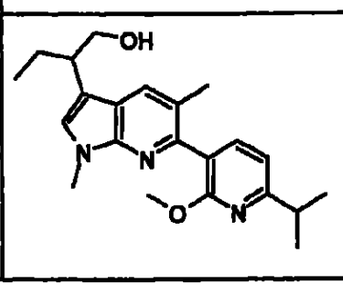
460		2 [3-(6-isopropil-2 metoxi-piridin-3-il)-2 5-dimetil-5H pirrolo[2 3-b]pirazin-7-il]-propa 1-ol	355 16	1 76
461		Éste de 2-[3-(6-isopropil-2-metoxi-piridi -3-il)-2 5-dimetil-5H pirrolo[2 3-b]pirazin-7 il]-propil d ácido meta lfónico	433 07	1 77
462		3-(6-isopropil-2 metoxi-piridi -3-il)-7-(2 metoxi-1 metil-etil)-2 5-dimetil-5H pirrolo[2 3-b]pira ina	369 15	1 83
463		3-(6-isopropil-2 metoxi-piridin-3-il)-2 5-dimetil-7 (1 metil-2-m rfolin-4-il-etil)-5H pirrolo[2 3-b]pirazina	424 13	1.53
464		7-sec-Butil-3-(6-isopropil-2-metoxi-piridin-3-il)-2 5-dimetil-5H pirrolo[2 3-b]pira ina	353 18	1 89

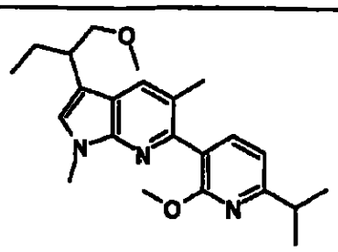
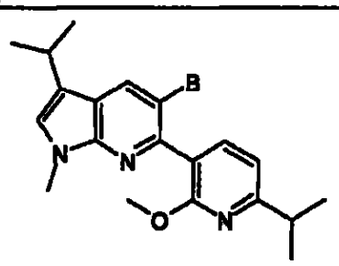
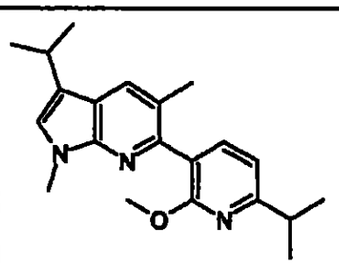
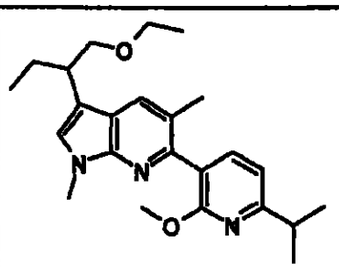
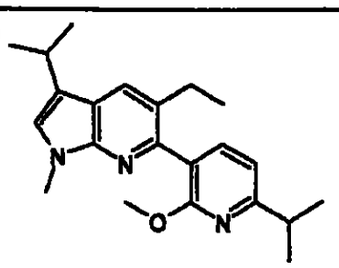
465		7 isopropil-3-(6-isopropil-2-metoxi-piridin-3-il)-2 5-dimetil-5H pirrolo[2 3-b]pirazina	339 19	1 87
466		2-[3-(6-isopropil-2-metoxi-piridin-3-il)-2 5-dimetil-5H pirrolo[2 3-b]pirazin-7-il]-butan-1-ol	369 15	1 78
467		3-(6-isopropil-2 metoxi piridi -3-il)-7-(1 metoximetil-propil)-2 5-dimetil-5H-pirrolo[2 3-b]pirazina	383 16	1 85
468		Éster d 2-[3-(6-isopropil-2 metoxi-piridin-3-il)-2 5-dimetil-5H-pirrolo[2 3-b]pirazin-7-il]-butilo de àcid metasulfónico	447 06	1 78
469		2-Etil-7-isopropil-3-(6-isopropil-2 metoxi-piridin-3-il)-5-metil-5H pirrolo[2 3-b]pirazi	353 18	1 92

470		3-(2-Etil-6-isopropil-piridin-3-il)-7 (2-metoxi-1-metil-etil)-2 5-dimetil-5H-pirrolo[2 3-b]pirazina	367 18	1.36
471		2 Etil-3-(2-etil-6-isopropil-piridin-3-il) 7-isopropil-5-metil-5H-pirrolo[2 3-b]pirazi	351 24	1 70
472		[3-(2-Etil-7 isopropil-5-metil-5H pirrolo[2 3-b]pirazin-3-il)-6-isopropil-piridin-2-il]-metil-mi	352.21	1 50
473		(6-Isopropil-3-[7-(2 metoxi-1 metil-etil)-2 5-dimetil-5H-pirrolo[2 3-b]pirazin-3-il]-piridin-2-il}-metil-aml	368 19	1.37
474		(4-Etil-5-[2-etil 7 (1-etil-propil)-5-metil-5H-pirrolo[2 3-b]pirazin-3-il] pirldi 2-il}-dimetil-amina	380.5	

475		Etil-[4-etil-5-[2-etil-7-(1-etil-propil)-5-metil-5H-pirrolo[2 3-b]pira in-3-il]-piridin-2-il]-metil-ami	394 5	
476		2 2' Dietil-7 7 -bis-(1 etil-propil)-5 5 dimetil-5H 5 H [3 3']bi[pirrolo[2 3-b]pirazi il]	461.30	1 97
477		5-Etil-6-[2-etil-7-(1 etil-propil)-5-metil-5H-pirrolo[2 3-b]pirazi -3-il]-3-isopropil-3H-imidazo[4 5-b]piridi	419 38	1 78
478		2-Etil-7-(2-metoxi-etil)-3-(2-metoxi-4-trifl rometoxi-fe il)-5-metil-5H-pirrolo[2 3-b]pirazina	410 06	

479		3-[2-Etil-3-(2-metoxi-4-trifl orometoxi-fenil)-5-metil-5H pirrolo[2 3-b]pirazin-7-il]-propio itril	405 07	
480		5-Bromo-3-(1-etil-propil)-6-(2-metoxi-4-trifluorometoxi-fenil)-1-metil-1H pirrolo[2 3-b]piridi		
481		3-(1 Etil-propil)-6-(2-metoxi-4-trifl orometoxi-fenil)-1 5-dimetil 1H-pirrolo[2 3-b]piridina	407 6	
482		5-Cloro-3-(1-etil-propil)-6-(2-metoxi-4-trifluorometoxi-fe il)-1-metil-1H-pirrolo[2 3-b]piridina		

483		3-1 Etil-propil)-6-(2-metoxi-4-trifl rometoxi-fenil-1 5-dimetil-1H-pirrolo[2 3-b]piridi	407 6	
484		3-sec-Butil-6-(6-isopropil-2-metoxi-piridin-3-il)-1 5-dimetil-1H-pirrolo[2 3-b]piridin	352 5	
485		3-sec-Butil-6-(2-etil-6-isopropil-piridi -3-il)-1 5-dimetil 1H pirrolo[2 3-b]piridi	350.5	
486		[3-(3-sec-Butil-1 5-dimetil-1H pirrolo[2 3-b]piridi 6-il}-6-isopropil-piridin-2-il]-metil-mina	351 4	
487		2-[6-(6-Isopropil-2 metoxi-piridin-3-il}-1 5-dimetil-1H pirrolo[2 3-b]piridin-3-il butan-1 ol	368.3	

488		6-(6-Isopropil-2 metoxi-piridin-3-il)-3-(1-metoximetil-prop l)-1 5-dimetil 1H-p rrolo[2 3-b]piridi	382.3	
489		5-Bromo-3-isopropil-6-(6-isopropil-2-metoxi-piridin-3-il)-1 metil-1H pirrol [2 3-b]piridi	402 5	
490		3-Isopropil-6-(6-isopropil-2-metoxi-piridin-3-il)-1 5-dimetil-1H pirrolo[2 3-b]piridi	338 3	
491		3-(1 Etoximetil-propil)-6-(6-isopropil 2-metoxi-piridin-3-il)-1 5-dimetil-1H-pirrolo[2 3-b]piridi	396 5	
492		5-Etil-3-isopropil-6-(6-isopropil-2 metoxi-piridi -3-il)-1-metil-1H-pirrolo[2 3-b]piridina	352 17	3 14

Ejemplo 51

Ensayo para la actividad de unión del receptor CRF

Como se discutió anteriormente el siguiente ensayo se define aquí como un ensayo de unión de receptor CRF in Vitro estándar

La utilidad farmacéutica de los compuestos de esta invención se indica por el siguiente ensayo para *actividad del receptor* CRF1 *La unión del receptor* CRF se desarrolla utilizando una versión modificada del ensayo descrito por Grigoriadis y De Souza (Méthods in Neurosciences Vol 5 1991) Las células de neuroplastoma humano IMR 32 una línea celular que expresa naturalmente el receptor CRF1 crecen Medio IMR 32 que consiste de EMEM w/Earle s BSS(JRH Biosciences Cat#5141)mas como complementos 2mM L-Glutamina 10% de suero Bovino fetal 25 mM de HEPES (pH 7 2) 1 mM de Piruvato de sodio y aminoácidos no esenciales (JRH Biosciences Cat# 58572) Las células crecen para confluencia y se dividen tres veces (todas la divisiones y cosechas se llevan a cabo utilizando NO ZYME JRH Biosciences Cat#59226) Las células se dividen primero 1 2 se incuban durante 3 días y se dividen 1 3 y finalmente se incuban durante 4 días y se dividen 1 5 Las células se incuban luego durante 4 días adicionales antes de ser diferenciadas mediante tratamiento con 5-bromo-2 desoxiuridina (BrdU Sigma Cat# B9285) El medio se remplaza cada 3-4 días con medio IMR-32 w/2 5uM BrdU y las células se cosechan 10 días después de tratamiento con BrdU y se lavan con PBS libre de Magnesio y calcio

Para preparar las células de membranas que contienen receptores se homogenizan en amortiguador de lavado (50mM Tris HCL 10 mM $MgCl_2$ 2 mM EGTA pH 7 4) y se centrifugan a 48 000 x g por 10 minutos a 4 C El granulo se

resuspende en amortiguador de lavado y la etapa de centrifugación y homogenización se desarrollan dos veces adicionales

Los gránulos de membrana (que contienen receptores CRF) se resuspenden en 50 mM de amortiguador Tris (pH 7 7 que contiene 10 mM de $MgCl_2$ y 2 mM EDTA y se centrífuga durante 10 minutos a 48 000 g Las membranas se lavan de nuevo y se llevan a una concentración final de 1500 ug/ml en amortiguador de unión (amortiguador Tris sobre 0 1 % BSA 15 mM bacitracin y 0 01 mg / ml de aprotonina) Para el ensayo de unión se agrega 100 ul de preparación de membrana a placas de micro tubos de 96 pozos que contienen 100 ul de ^{125} I CRF (SA 2200 Ci/mmol concentración final de 100 pM) y 50 ul del compuesto de ensayo La unión se lleva a cavo a temperatura ambiente durante 2 horas

Las placas luego se cosechan en un cosechador de célula de 96 pozos BRANDEL y los filtros se cuentan para emisiones gama en un contador de centelleo de liquido BETAPLATE1205 wallac La unión no especifica se define por 1 mM de CRF frío Los valores IC_{50} se calculan con el programa de ajuste de curva no lineal RS/1 (BBN Sofrware Products Corp Cambridge MA) La afinidad de unión para los compuestos de formula I expresado como el valor IC_{50} generalmente varia de cerca 0 5 nanomolar a cerca de 10 micro molar Los compuestos preferidos de la formula I exhiben valores IC_{50} de menos de o igual a 1 5 micro molar compuestos más prefendos de la formula I y exhiben valores IC_{50} de menos de 500 nanomolar todavía compuestos más prefendos de la formula I exhiben valores IC_{50} de menos de 100 nanomolar y compuestos más preferidos de la formula I exhiben valores de IC_{50} de menos de 10 nanomolar Los compuestos mostrados en los ejemplos 1-33 se han probado en este ensayo y se encuentra que exhiben valores IC_{50} de menos de o igual a 4 micro molar

Ejemplo 52

Preparación de compuestos de sonda radió etiquetada de la invención

Los compuestos de la invención se preparan como sondas radió etiquetadas para llevar a cabo dentro de precursores que utilizan síntesis que comprenden al menos un átomo que es un radioisótopo El radioisótopo se selecciona preferiblemente de al menos uno de carbono (preferiblemente ^{14}C) Hidrógeno (preferiblemente ^{3}H) azufre (preferiblemente ^{35}S) o yodo (preferiblemente ^{135}I Tales ondas radio etiquetadas se sintetizan convenientemente mediante un proveedor de radioisótopo que se especializa en las síntesis habitual de compuestos de sonda radio etiquetada Tales proveedores incluyen Amersham Corporation Arlington Heights IL Cambridge Isotope Laboratories Inc Andover MA SRI International Menlo Park CA Wizard Laboratories West Sacramento CA ChemSyn Laboratories Lexena KS American Radiolabeled Chemicals Inc St Louis MO y Moravek Biochemicals Inc Brea CA

Los compuestos de sonda radio etiquetados con tridio también se preparan convenientemente en forma catalítica por vía de intercambio catalizado con platino en ácido acético tridiado el intercambio catalizado por ácido en ácido trifluroacético tritiado o intercambio catalizado heterogéneo con gas de tritio Tales preparaciones también se llevan a cabo convenientemente como un radio etiquetado habitual mediante cualquiera de los proveedores listados en el párrafo anterior que utilizan el compuesto de la invención como sustrato Adicionalmente ciertos precursores se pueden someter a intercambio de alógeno-tritio con gas de tritio reducción de gas de tritio de enlaces no saturados o reducción que utiliza boro tritio de sodio según sea apropiado

Ejemplo 53

Auto radiografía de receptor

La autoradiografía de receptor (mapeo de receptor) se lleva a cabo in Vitro como se describe por Kuhar en las secciones 8 1 1 a 8 1 9 de Current Protocols in Pharmacology (1998) John Wiley & Sons New York utilizando compuesto radio etiquetados de la invención preparados según se describe en los ejemplos precedentes

Ejemplo 54

Aspectos adicionales de compuestos preferidos de la invención

Los compuestos más preferidos de la invención son adecuados para uso farmacéutico en tratamiento en pacientes humanos De acuerdo con esto tales compuestos preferidos no son tóxicos Ellos no exhiben dosis multiples o sencilla aguda o toxicidad a largo plazo mutagenicidad (por ejemplo como se determina en ensayos de mutación reversa bacteriana tal como en ensayos Ames) teractogenicidad tumorgenicidad o similares y efectos adversos que se disparan raramente (efectos colaterales) cuando se administran en dosis terapéuticamente efectivas

Preferiblemente la administración de tales compuestos preferidos de la invención en ciertas dosis (es decir dosis que producen efecto terapéutico en concentraciones in vivo o preferiblemente dosis de 10 50 100 150 o 200 mg/Kg administrados parenteralmente o preferiblemente en forma oral) no resulta en la prolongación de intervalos QT de corazón (es decir como se determinan mediante electrocardiografía por ejemplo en conejillos de india cerditos o perros

Cuando se administra diariamente durante 5 o preferiblemente 10 días tales dosis de tales compuestos preferidos tampoco originan agrandamiento del hígado que resulta en un incremento de la proporción de peso corporal del hígado de más del 100 % preferiblemente no más de 75% y más preferiblemente no más del 50% sobre los controles emparejados en roedores de laboratorio (por ejemplo ratones o ratas) En otro aspecto tales dosis de tales compuestos preferidos tampoco origina preferiblemente agrandamiento del hígado resultante en un incremento de la proporción de peso corporal del hígado de más de 50% como preferiblemente no más de 25% y más preferiblemente no más de 10% sobre controles emparejados no tratados en perros u otros mamíferos no roedores

En aún otro aspecto tales dosis de tales compuestos preferidos tampoco promueven preferiblemente la liberación de enzimas del hígado (por ejemplo ALT LDH O AST) de hepatocitos in vivo Preferiblemente tales dosis no elevan los niveles de suero de tales enzimas por más del 100% preferiblemente no más del 75 % y más preferiblemente no más del 50% sobre los controles no tratados emparejados en roedores de laboratorio De forma similar las concentraciones (en medios de cultivo u otras soluciones que se conectan e incuban con células in Vitro) equivalentes a dos veces preferiblemente cinco veces y más preferiblemente diez veces la concentración terapéutica mínima in vivo que no origina liberación de ninguna de tales encimas del hígado de hepatocitos dentro de medio de cultivo in Vitro por encima de los niveles de línea base vistos en medios de células no tratadas

Debido a los efectos colaterales que se deben a menudo a la activación del receptor o antagonismo indeseado los compuestos preferidos de la invención ejercen sus efectos moduladores de receptor con alta selectividad Estos medios

que no se unen a ciertos otros receptores (diferentes a los receptores CRF) con alta afinidad pero solo para activar o inhibir la actividad de tales otros receptores con constantes de afinidad de más de 100 nanomolar preferiblemente mayores de 1 micro molar más preferiblemente mayores de 10 micro molar y más preferiblemente mayores de 100 micro molar Tales receptores preferiblemente se seleccionan a partir del grupo que incluye receptores de canal de Ion que incluyen receptores de canal de Ion de sodio receptores neuro transmisores tales como receptores alfa y beta ad enérgicos receptores muscarínicos (particularmente receptores m1 m2 y m3) receptores dopamina y receptores de glutamato metabotrópico y también incluyen receptores de histamina y receptores de citoquina por ejemplo receptores de interleuquína particularmente receptores IL 8 El grupo de otros receptores a los que los compuestos preferidos no se unen con alta afinidad también incluyen receptores GBA_A receptores de péptido bioactivo (que incluye receptores NPY y VIP) receptores de neurõquimina receptores de bradiquinina (por ejemplo receptores BK1 y receptores BK2) y receptores de hormona (que incluyen receptores de hormona de liberación de tirotropina y receptores de hormona que concentran melanocitos)

Ejemplo 55

Ausencia de Actividad de Canal de Ion de Sodio

Los compuestos preferidos de la invención no exhiben actividad como bloqueadores de canal de Ion de sodio La actividad del canal de sodio se puede medir como ensayos de unión de canal de sodio in Vitro estándar tales como el ensayo dado por Brown et al (J Neurosci 1986 265 17995 18004) Los compuestos preferidos por la invención exhiben menos de 15% de inhibición y más preferiblemente menos de 10% de inhibición de unión de ligando de

específico de canal de sodio cuando está presente en una concentración de 4 uM El ligando específico canal de Ion de sodio utilizado puede ser batracotoxinina etiquetada tetrodotoxina o saxitoxina Tales ensayos que incluyen el ensayo de Brown mencionado anteriormente se desarrollan como un servicio comercial de CEREP Inc Redmond WA

Alternativamente la actividad del canal de Ion de sodio se puede medir in vivo en un ensayo de actividad antiepiléptica La actividad antiepiléptica de los compuestos se puede medir mediante la capacidad de los compuestos para inhibir la extensión de la extremidad trasera en modelos de choque eléctrico supramaximales Ratas Wistar Han machos (150 200 mg) se dosifican i p con una suspensión de 1 a 20 mg del compuesto de ensayo en 0 25 % de metilcelulosa 2 hr antes de ensayo Se lleva a cabo una observación visual justo antes de ensayar para la presencia de ataxia Utilizando electrodos auriculares se aplica una corriente de 200 mA de duración de 200 milisegundos y la presencia o ausencia de la extensión de la extremidad trasera se nota Los compuestos preferidos de la invención no exhiben actividad antiepiléptica significativa en el nivel p< 0 1 de significancia o más preferiblemente en el nivel p< 0 05 de significancia como se mide utilizando un ensayo paramétrico estándar de importancia estadística tal como un ensayo de T student's

Ejemplo 56

Vida media in Vitro microsomal

Los valores de vida media de compuesto (valores $t_{1/2}$) se pueden determinar por vía del siguiente ensayo de vida media microsomal del hígado estándar Se obtienen microsomas de hígado humano agrupadas de XenoTech LLC 3800

Cambridge St Kansas s City Kansas 66103(Catalog #H0610 Tales microsomas de hígado también se pueden obtener de in Vitro Technologies 1450 South Rolling Road Baltamore MD 21227 o de Tissue Transformation Technologies Edison Corporate Center 175 May Street Suite 600 Edison NJ 08837 Las reacciones se desarrollan como sigue

Reactivos +

Amortiguador de Fosfato 19 mL $NaH_2PO_4$0 1 M 81 mL 0 1 Na_2HPO_4 ajustado a pH H_3PO_4

Mezcla de Cofactor 16 2 mg NADP 450 4 mg de Glucosa-6-fosfato en 4 mL 100 mM de $MgCl_2$

Deshidrogenasa Glucosa-6-fosfato Suspensión de 214 3 ul glucosa –6 fosfato deshidrogenasa (Boehringer Manheim catalog no 0737224 distribuido por Roche Molecular Biochemicals 9115 Hague Road P O Box 50414 Indianápolis IN 46250) se diluye en 1285 7 ul de agua destilada

Inicio de mezcla de Reacción Mezcla de 3 mL de CoFactor 1 2 mL Glucosa-6 fosfato Deshidrogenasa

Reacción

Se prepararon 6 reacciones de ensayo cada una contiene 25 ul de microsomas 5 ul de una solución de 100 uM de compuesto de ensayo y 399 ul de 0 1 de amortiguador de fosfato Una séptima reacción se preparada como un control

positivo que contiene 25 ul de microsomas 399 ul 0 1 M de amortiguador de fosfato y 5 ul de una solución de 100 uM de un compuesto con unas propiedades metabólicas conocidas (por ejemplo DIAZEPAM o CLOZEPINE Las reacciones se preincuban a 39 C durante 10 minutos 71 ul de mezcla de reacción de partida se agrega a 5 de las 6 reacciones de ensayo y al control positivo 71 ul 100 mM de $MgCl_2$ se agrega a la sexta reacción de ensayo que se utiliza como un control negativo En cada punto de tiempo (0 1 3 5 y 10 minutos) 75 ul de cada mezcla de reacción se pipetea dentro de un pozo de una placa de 96 pozos que contiene 75 ul de acetonitrilo enfriado con hielo Las muestras se mezclan y centrifugan 10 minutos a 3500 rpm (Solval T 6000D centrifuge H1000B rotor 75 ul de súper nadante de cada reacción se trasfiere a un pozo de una placa de 96 pozos que contiene 150 ul de una solución de 0 5 uM de un compuesto con un perfil LCMS conocido (estándar interno) por pozo Análisis LCMS de cada muestra se llevo a cabo y la cantidad de compuesto de ensayo no metabolizado se mide como AUC la concentración del componente versus el tiempo se grafica y el valor $t_{1/2}$ del compuesto de ensayo se extrapola

Los compuestos preferidos de la invención exhiben valores in Vitro $t_{1/2}$ de más de 10 minutos y menos de 4 horas Los compuestos más preferidos de la invención exhiben valores in Vitro $t_{1/2}$ de entre 30 minutos y 1 hora en microsomas de hígado humano

Ejemplo 57

Ensayo de Toxicidad MDCK

Los compuestos que originan cito toxicidad aguda se reducen en la producción de ATP mediante células de riñón canino Madin Darby (MDCK) en el siguiente ensayo

Las células MDCK ATCC no CCL 34 (American Type Culture Collection Manassas VA) se mantienen en condiciones estériles luego de las instrucciones en la hoja de información de producción ATC El PACKARD (Menden CT) ATP LITE M Luminescent ATP detection Kit No Producto 6016941 permite la medición de producción ATP en células MDCK

Antes de ensayar 1 ul de compuesto de ensayo o muestra de control se pipetea en PACKARD (Menden CT) placas de 96 pozos de fondo claro Los compuestos y las muestras de control se diluyen en DMSO para dar una concentración final en el ensayo de 10 micromolar 100 micromolar o 200 micromolar Las muestras de control son drogas u otros compuestos que tienen propiedades de toxicidad conocidas

Las células MDCk confluente se tripsinizan se cosechan y se diluyen a una concentración de 0 1 x 10^6 células/ml con medio caliente (37 C) VITACELL Minimum Essential Médium Eagle (ATCC catalogo # 30 2003) 100ul de células en medio se pipetean en cada uno de todos los pozos de las placas de 96 pozos excepto cinco Las células sin medio caliente (100ul) se pipetean en los cinco restantes pozos de cada placa para suministrar pozos de control de curva estándar Estos pozos a los que no se agregan células se utilizan para determinar la curva estándar Las placas se incuban luego a 37 C durante 95% de O_2, 5% de CO_2 durante 2 horas con agitación constante Después de incubación 50 ul de la solución de lysis de célula de mamífero se agrega por pozo los pozos se cubren con stickers PACKARD TOPSEAL y las placas se agitan a aproximadamente 700 rpm en una agitador adecuado durante 2 minutos

Durante la incubación los reactivos PACKARD ATP LITE M se les permite equilibrar a temperatura ambiente Una vez equilibrados la solución de sustrato liofilizada se reconstituye en 5 5 mls de solución de amortiguador de sustrato (del kit) La solución estándar ATP liofilizada se reconstituye en agua desionizada para dar un depósito de 10 mM Para los cinco pozos de control 10 ul de PACKARD estándar diluidos serialmente se agrega a cada uno de los cinco pozos de control de curva estándar para producir una concentración final en cada pozo posterior de 200 nM 100 nM 50 nM 25 nM y 12 05 nM

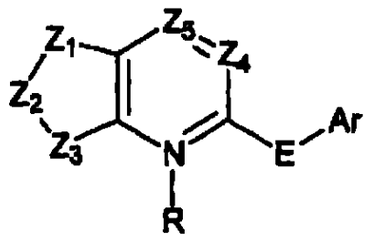
La solución de sustrato PACKARD (50 ul) se agrega a todos los pozos Los pozos se cubren con stickers PACKARD TOPSEAL y las placas se agitan a aproximadamente 700 rpm en un agitador adecuado durante 2 minutos Un sticker PACKARD blanco se adhiere al fondo de cada placa y las muestras oscuras se adaptan por placas que se envuelven en hojas y se colocan en la oscuridad durante 10 minutos Luego se mide la luminiscencia a 22 C utilizando un contador de luminiscencia por ejemplo PACKARD TOPCOUNT Microplate Scintillation and Luminescense Counter o TECAN SPETRAFLUOR PLUS

Los valores de luminiscencia en cada concentración de droga se comparan con los valores computados de la curva estándar para esa concentración Los compuestos de ensayo preferidos exhiben valores de luminiscencia de 80 % o más del estándar o preferiblemente 90 % o más del estándar cuando una concentración de 10 micro molar (uM) del compuesto de ensayo se utiliza Cuando una concentración de 100 uM de compuesto de ensayo se utiliza los compuestos de ensayo preferidos exhiben valores de luminiscencia de 50% o más del estándar o más preferiblemente 80% o más del estándar

LO QUE SE REIVINDICA ES

REIVINDICACIONES

1 Un compuesto de la Fórmula I-a



I-a

o las sales farmacéuticamente aceptables de estos en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1 C_4

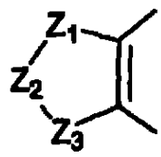
m es 0 1 o 2

Ar se escoge de

fenilo que es mono- di o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido y heteroarilo opcionalmente mono- di o tri-sustituido dicho heteroarilo tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a 3 heteroátomos seleccionado del grupo que consiste de N O y S

R es oxígeno o está ausente

el grupo



representa un sistema de anillo de 5 miembros saturado insaturado o aromático que contiene 0 o 1 heteroátomos en donde

Z_1 es CR_1 o CR_1R_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 o CR_3R_3

R_1 se escoge de hidrógeno halógeno hidroxi ciano amino alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido alcoxi opcionalmente sustituido mono o dialquilamino opcionalmente sustituido cicloalquilo opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido alquiltio opcionalmente sustituido alquilsulfinilo opcionalmente sustituido alquilsulfonilo opcionalmente sustituido mono-o dialquilcarboxamida opcionalmente sustituida anlo carbocíclico opcionalmente sustituido heterociclo opcionalmente sustituido y heteroarilo opcionalmente sustituido dicho heterociclo o heteroarilo opcionalmente sustituido tienen de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionado del grupo que consiste de N O y S

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo haloalquilo alcoxi aminoalquilo hidroxialquilo

y mono y dialquilamino en donde cuando R_1 o R_1 es alquilo opcionalmente sustituido entonces R_3 es alquilo $C_{1\ 3}$ opcionalmente sustituido

R_1 R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo haloalquilo y aminoalquilo

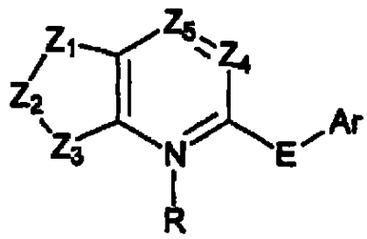
R_2 se escoge de hidrógeno alquilo opcionalmente sustituido alquilo opcionalmente sustituido y aminoalquilo opcionalmente sustituido

Z_4 es NR o CR_4

Z_5 es NR o CR_5

R_4 y R_5 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido alcoxi opcionalmente sustituido mono o dialquilamino opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido alquiltio opcionalmente sustituido alquilsulfinilo opcionalmente sustituido alquilsulfonilo opcionalmente sustituido mono-o dialquilcarboxamida opcionalmente sustituida anlo carbocíclico opcionalmente sustituido y heteroanlo opcionalmente sustituido dicho heteroanlo opcionalmente sustituido tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a cerca de 3 heteroátomos seleccionados del grupo que consiste de N O y S

2 Un compuesto de la Fórmula I-a



I-a

o las sales farmacéuticamente aceptables de estos en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

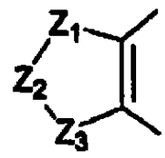
R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1-C_4

m es 0 1 o 2

Ar se escoge de

fenilo que es mono- di- o tri-sustituido con R_A y 1 naftilo 2 naftilo pirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono di- o tri-sustituido con R_A

el grupo



representa un sistema de anillo saturado insaturado o aromático que comprende 0 o 1 heteroátomos en donde

Z_1 es CR_1 o CR_1R_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 o CR_3R_3

R_1 se escoge de

i) hidrógeno halógeno hidroxi ciano amino alquilo C_1 C_{10} O(alquil C_1 C_6) mono o di(alquil C_1-C_6)amino (cicloalquil C_3 C_7) alquilo C_1 C_4 halo (C_1 C_6) alquilo O(halo (C_1 C_6) alquilo) y S(O) (alquilo C_1 C_6) O(cicloalquilo C_3 C_7) alquilo C_1 C_4 y S(O) (alquilo C_1-C_6) donde cada alquilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono- o di (C_1 C_4) alquilamino

y

donde cada cicloalquilo C_3 C_7 es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1 C_4 y mono-o di (C_1 C_4) alquilamino y

ii) fenilo que es mono- di o tri-sustituido con R_A 1 naftilo 2 naftilo pirídilo dihidropirídilo tetrahidropirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales es opcionalmente mono- di- o tri sustituido con R_A

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1 C_3 halo (C_1 C_3) alquilo alcoxi C_1 C_3 amino (C_1 C_3) alquilo y mono y di (C_1-C_6) alquilamino

R_1 R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1-C_6 halo (C_1 C_6) alquilo y amino (C_1 C_6) alquilo

R_2 se escoge de hidrógeno alquilo C_1 C_6 halo (C_1-C_6) alquilo y amino (C_1-C_6) alquilo

Z_4 es NR o CR_4

Z_5 es NR o CR_5

en donde Z_4 y Z_5 no son ambos NR

R_4 y R_5 son independientemente escogidos de hidrógeno halógeno ciano nitro amino mono o di (carbhidrilo C_1 C_6) amino carbhidrilo C_1 C_6 (ciclocarbhidrilo C_3-C_7) carbhidrilo C_0-C_4 O(ciclocarbhidrilo C_3 C_7) halo(C_1 C_6) carbhidrilo -O(halo (C_1-C_6)carbhidrilo -O(carbhidrilo C_1-C_6) y S(O) (carbhidrilo C_1 C_6) donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1 C_4 y mono- y di (C_1 C_4) alquilamino

y

donde cada carbhidrilo C_3-C_7 es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1-C_4 y mono y di (C_1-C_4) alquilamino

R_A es independientemente seleccionada en cada ocurrencia de halógeno ciano nitro halo (C-C_6) alquilo halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1-C_6 sustituido con 0 2 R_B alquenilo C_2-C_6 sustituido con 0-2 R_B alquinilo C_2-C_6 sustituido con 0 2 R_B cicloalquilo C_3-C_7 sustituido con 0 2 R_B (cicloalquilo C_3-C_7) alquilo C_1-C_4 sustituido con 0 2 R_B alcoxi C_1-C_6 sustituido con 0 2 R_B NH(alquilo C_1-C_6) sustituido con 0-2 R_B N(alquilo

C_1-C_6)(alquilo C_1 C_6) cada alquilo C_1 C_6 independientemente sustituido con 0 2 R_B XR_c y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1 C_4 -O(alquil C_1-C_4) NH(alquilo C_1-C_4) N(alquilo C_1 C_4)(alquilo C_1-C_4) S(O)n(alquilo) halo (C_1 C_4) alquilo halo(C_1-C_4) alcoxi CO(alquilo C_1 C_4) CONH(alquilo C_1 C_4) CON(alquilo C_1 C_4)(alquilo C_1-C_4) XR_C y Y

Rc y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia

hidrógeno y grupos alquilo rectos ramificados o cíclicos que incluyen grupos (cicloalquil) alquilo que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contienen cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituido con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1 C_6 NH(alquilo C_1 C_6) N(alquilo C_1 C_6)(alquilo C_1-C_6) NHC(=O)(alquilo C_1 C_6) N(alquilo C_1 C_6)C(=O)(alquilo C_1-C_6) NHS(O) (alquilo C_1-C_6) -S(O) (alquilo C_1 C_6) S(O) NH(alquilo C_1 C_6) S(O) N(alquilo C_1 C_6)(alquilo C_1-C_6) y Z

X es independientemente seleccionado en cada ocurrencia del grupo que consiste de CH2 CHR_D- -O C(=O) -C(=O)O S(O) NH NR_D- C(=O)NH C(=O)NR_D- S(O) NH -S(O) NR_D- -OC(=S)S- NHC(=O)

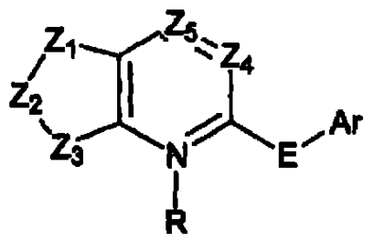
$NR_DC(=O)$ NHS(O) $-OSiH_2-$ OSiH(alquilo C1 C4) -OSi (alquilo C_1 C_4)(alquilo C_1 C_4) y $NR_DS(O)$

Y y Z son independientemente seleccionado en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituido con uno o más sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino ciano alquilo C_1 C_4 O(alquilo C_1 C_4) NH(alquilo C_1 C_4) N(alquilo C_1 C_4)(alquilo C_1 C_4) y S(O) (alquilo)

en donde dicho grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S con el punto de unión siendo el carbono o nitrógeno

y n es independientemente seleccionado en cada ocurrencia de 0 1 y 2

3 Un compuesto de Fórmula I b



Fórmula I b

o una sal farmacéuticamente aceptable de estos en donde

E es un enlace simple O $S(O)_m$ NR NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1 C_4

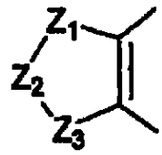
m es 0 1 o 2

R es oxígeno o está ausente

Ar se escoge de

fenilo que es mono- di o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido y opcionalmente heteroarilo mono di o tri-sustituido dicho heteroarilo tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionado del grupo que consiste de N O y S

el grupo



representa un sistema de anillo saturado insaturado o aromático que comprende 0 o 1 heteroátomos en donde

Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es CR_2 o CR_2R_2

Z_3 es CR_3 CR_3R_3 o NR_3

R_1 y R_1 son escogidos de hidrógeno alquiloC_1-C_{10} alquenilo C_2-C_{10} alquinilo C_2-C_{10} cicloalquilo C_3 C_7 (benzo) cicloalquilo C_3 C_7 (cicloalquil C_3-C_7) alquilo C_1 C_4 heterocicloalquilo C_{3-9} (heterocicloalquilo C_{3-9}) alquilo C_1 C_4 (benzo) heterocicloalquilo C_{3-9} ((benzo) heterocicloalquilo C_{3-9}) alquilo C_1 C_4 y halo (C_1-C_8) alquilo cada uno de los cuales es sustituido con 0 o más sustituyentes independientemente escogidos de halógeno hidroxi amino

oxo ciano alquilo C_1 C_6 alcoxi C_1 C_6 halo alcoxi C_1 C_6 alcanoilo C_1-C_6 alcanoiloxi C_1-C_6 alcoxicarbonilo C_1 C_6 N (alcanoilo C_1-C_6) N (alquil C_0-C_6) amino N (alcanoiloxi C_1-C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1-C_6) N (alquil C_0-C_6) amino alquilsulfonamida C_1 C_6 alquilsulfonilo C_1 C_6 alquilsulfoniloxi C_1 C_6 hidroxialquilo C_1 C_6 alcoxi C-C_6 alquilo C_1-C_6 haloalcoxi C_1-C_6 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono-y di (C_1 C_6) alquilamino N (alcanoilo C_1 C_6) N (alquil C_0-C_6) amino N-(alcanoiloxi C_1 C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1-C_6) N (alquil C_0-C_6) amino mono y di (C_1-C_6) alquilcarbamoilo XR_C y X Z con la condición que R_1 y R_1 no sea alquilo sustituido con arilo o heteroarilo

R_2 se escoge de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1 C_3 halo (C_1-C_3) alquilo alcoxi C_1 C_3 amino (C_1 C_3) alquilo y mono y di (C_1-C_6) alquilamino

R_3 se escoge de hidrógeno hidroxi amino halógeno ciano nitro alquilo C_1 C_3 halo (C_1-C_3) alquilo alcoxi C_1 C_3 amino (C_1 C_3) alquilo hidroxi (C_1-C_3) alquilo ciano (C_1 C_3) alquilo y mono y di (C_1 C_3) alquilamino

R_3 se escoge de hidrógeno hidroxi amino alquilo C_1 C_3 halo (C_1 C_3) alquilo alcoxi C_1-C_3 amino (C_1 C_3) alquilo hidroxi (C_1-C_3) alquilo ciano (C_1 C_3) alquilo y mono y di (C_1 C_3) alquilamino

R_1 R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1 C_6 halo (C_1 C_6) alquilo y amino (C_1 C_6) alquilo

Z_4 es NR o CR_4

Z_5 es NR o CR_5

R_4 y R_5 son independientemente escogidos de hidrógeno halógeno ciano nitro amino mono o di (carbhidrilo C_1 C_6)amino carbhidrilo C_1 C_6 (ciclocarbhidrilo C_3 C_7) carbhidrilo C_0-C_4 -O(ciclocarbhidrilo C_3 C_7) halo (C_1 C_6) carbhidrilo O(halo (C_1-C_6) carbhidrilo) O(carbhidrilo C_1-C_6) S(O)n(carbhidrilo C_1-C_6) y heterocicloalquilo de 4 a 7 miembros donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triples enlaces y es opcionalmente sustituido con una o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono y di (C_1-C_4) alquilamino

y

donde cada carbhidrilo C_3 C_7 heterocicloalquilo es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno amino hidroxi oxo ciano alcoxi C_1-C_4 y mono- y di (C_1 C_4) alquilamino o

R_5 tomado en combinación con R_1 o R_1 forman un heterociclo de 5 a 9 miembros

R_A es independientemente seleccionado en cada ocurrencia de halógeno ciano nitro halo (C_1-C_6) alquilo halo (C_1 C_6) alcoxi hidroxi amino alquilo C_1 C_6 sustituido con 0 2 R_B alquenilo C_2-C_6 sustituido con 0-2 R_B alquinilo C_2-C_6 sustituido con 0-2 R_B cicloalquiloC$_3$ C_7 sustituido con 0-2 R_B (cicloalquil C_3 C_7) alquilo C_1-C_4 sustituido con 0-2 R_B alcoxi C_1-C_6

sustituido con 0-2 R_B NH (alquilo C_1 C_6) sustituido con 0-2 R_B N(alquilo C_1-C_6) (alquilo C_1 C_6) cada alquilo C_1-C_6 independientemente sustituido con 0-2 R_B XR_C y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1 C_4 O(alquilo C_1 C_4) NH (alquilo C_1 C_4) N(alquilo C_1 C_4)(alquil C_1 C_4) -S(O)n(alquilo) halo (C_1-C_4) alquilo halo (C_1 C_4) alcoxi CO(alquilo C_1 C_4l) CONH (alquilo C_1-C_4) CON(alquilo C_1-C_4) (alquilo C_1 C_4) XR_C y Y

R_C y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia de

hidrógeno y

grupos alquilo rectos ramificados o cíclicos que incluyen grupos (cicloalquil) alquil que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contiene cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituidos con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1 C_6 NH (alquilo C_1 C_6) N(alquilo C_1 C_6)(alquilo C_1 C_6) NHC(=O)(alquilo C_1 C_6) N(alquilo C_1 C_6)C(=O)(alquilo C_1-C_6) NHS(O) (alquilo C_1 C_6) S(O) (alquilo C_1 C_6) S(O) NH(alquilo C_1 C_6) S(O) N(alquilo C_1 C_6)(alquilo C_1 C_6) y Z

X es independientemente seleccionado en cada ocurrencia del grupo que consiste de -O C(=O)O -S(O) NH NR_D- C(=O)NH C(=O)NR_D-

S(O) NH S(O) NR_D- -OC(=S)S- NHC(=O) NR_DC(=O) NHS(O) $OSiH_2$- OSiH(alquilo C_1-C_4) OSi(alquilo C_1 C_4)(alquilo C_1-C_4) y NR_DS(O)

Y y Z son independientemente seleccionados en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituidos con uno o más sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino ciano alquilo C_1 C_4 -O(alquilo C_1 C_4) NH(alquilo C_1 C_4) N(alquilo C_1 C_4)(alquilo C_1 C_4) C(O)(alquilo C_1 C_4) y S(O) (alquilo) en donde dichos grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S el punto de unión es cualquier carbono o nitrógeno y

n es independientemente seleccionado en cada ocurrencia de 0 1 y 2

4 Un compuesto o sal de la reivindicación 3 donde

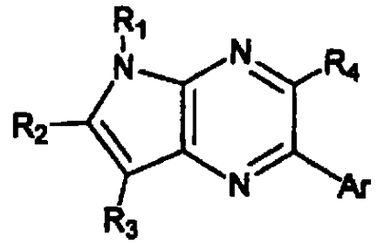
Ar se selecciona de

fenilo el cual es mono- di o tri sustituido con R_A y 1 naftilo 2 naftilo pirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono- di o tri-sustituido con R_A y

R_1 y R_1 son escogidos de alquiloC_1 C_{10} alquenilo C_2 C_{10} alquinilo C_2-C_{10} cicloalquilo C_3-C_7 (cicloalquilo C_3 C_7) alquilo C_1 C_4 heterocicloalquilo C_{3-8} (heterocicloalquilo C_{3-8}) alquilo C_1-C_4 y halo (C_1 C_8) alquilo cada uno de

los cuales es sustituido con 0 1 2 o 3 sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1-C_6 o alcoxi C_1-C_6 halo C_1-C_6 alcoxi alcanoilo C_1 C_6 alcanoiloxi C_1-C_6 alcoxicarbonilo C_1-C_6 N (alcanoilo C_1-C_6) N (alquil C_0-C_6)amino N (alcanoiloxi C_1 C_6) N (alquil C_0-C_6)amino N (alcoxicarbonilo C_1-C_6) N (alquil C_0-C_6)amino alquilo sulfonamida C_1 C_6 alquilosulfonilo C_1-C_6 alquilosulfoniloxi C_1 C_6 hidroxialquilo C_1 C_6 alcoxi C_1-C_6 alquilo C_1-C_6 haloalcoxi C_1 C_6 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono- y di- (C_1-C_6) alquilamino N (alcanoilo C_1-C_6) N (alquil C_0-C_6)amino N (alcanoiloxi C_1-C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1-C_6) N (alquil C_0-C_6)amino mono- y di (C_1 C_6) alquilcarbamoilo XR_C y X Z

5 Un compuesto o sal de acuerdo a la Reivindicación 3 de Fórmula II



Fórmula II

6 Un compuesto o sal de acuerdo con la Reivindicación 5 en donde

R_1 se define como la Reivindicación 3

R_2 se selecciona de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_3

R_4 se selecciona de hidrógeno halógeno ciano amino alquilo C_1-C_6 alcoxi C_1 C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1-C_4 (cicloalquilo C_3

C_7) alcoxi C_1 C_4 mono y di (alquilo C_1 C_6) amino amino(C_1 C_6) alquilo mono y di (alquilo C_1 C_6) amino (C C_6) alquilo halo (C_1 C_6) alquilo y halo (C_1 C_6)alcoxi y

Ar se selecciona del grupo que consiste de fenilo piridilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1 C_6) halo (C_1 C_6) alcoxi hidroxi amino alquilo C_1 C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 alcoxi C_1 C_6 mono- y di (alquilo C_1 C_6)amino amino (C_1-C_6) alquilo y mono- y di (alquilo C_1 C_6)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula II es sustituido

7 Un compuesto o sal de acuerdo con la Reivindicación 5 en donde

R_1 se selecciona de alquilo C_1C_{10} y (cicloalquilo C_3 C_7) alquilo C_0-C_4 cada uno de los cuales es sustituido con 0 o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alcoxi C_1 C4 y mono- y di (C_1 C_4) alquilamino

8 Un compuesto o sal de acuerdo con la Reivindicación 5 en donde

R_1 se selecciona de heterocicloalquilo C_{3-6} y (heterocicloalquilo C_{3-6}) alquilo C_1 C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1 C_6 alcoxi C_1-C_6 hidroxialquilo C_1 C_6 alcoxi C_1-C_6 alquilo C_1-C_6

haloalquilo(C_1 C_6) haloalcoxi(C_1-C_6) mono- y di (C_1 C_6) alquilamino XR_C

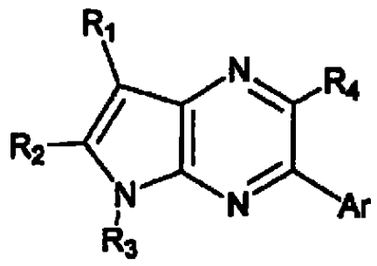
9 Un compuesto o sal de acuerdo con la Reivindicación 8 en donde

R_1 se selecciona de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales sustituido con de 0 a 2 sustituyentes independientemente seleccionados de

(i) halógeno hidroxi amino ciano o

(ii) (ii) alquilo C_1 C_4 alcoxi C_1-C_4 y mono- y di (C_1-C_4) alquilamino cada uno de los cuales sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-9}

10 Un compuesto o sal de acuerdo con la Reivindicación 3 de Fórmula VI



en donde R_1 R_2 R_3 y Ar son definidos como en la Reivindicación 3

11 Un compuesto o sal de acuerdo con la Reivindicación 10 en donde

R_1 se define como la Reivindicación 3

R_2 se selecciona de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_3

R_4 se selecciona de hidrógeno halógeno ciano amino alquilo C_1 C_8 alcoxi C_1-C_8 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 (cicloalquilo C_3 C_7) alcoxi C_1 C_4 mono y di (alquilo C_1-C_8) amino amino(C_1-C_8) alquilo mono y di (alquilo C_1 C_8) amino (C-C_8) alquilo halo (C_1 C_8) alquilo y halo (C_1-C_8)alcoxi y

Ar se selecciona del grupo que consiste de fenilo pirídilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1 C_8) halo (C_1 C_8) alcoxi hidroxi amino alquilo C_1-C_8 alquenilo C_2-C_8 alquinilo C_2 C_8 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 alcoxi C_1 C_8 mono- y di (alquilo C_1 C_8)amino amino (C_1-C_8) alquilo y mono- y di (alquilo C_1 C_8)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula VI es sustituido

12 Un compuesto o sal de acuerdo con la Reivindicación 11 en donde

R_1 se selecciona de alquilo C_1 C_{10} y (cicloalquilo C_3-C_{10}) alquilo C_0-C_4 cada uno de los cuales sustituido con 0 o más sustituyentes independientemente seleccionados de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono- y di (C_1 C_4) alquilamino

13 Un compuesto o sal de acuerdo con la Reivindicación 11 en donde

R_1 se selecciona de heterocicloalquilo C_{3-9} y (heterocicloalquilo C_{3-9}) alquilo C_1 C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1-C_6 alcoxi C_1 C_6 hidroxialquilo C_1 C_6 alcoxi C_1 C_6 alquilo C_1 C_6o haloalquilo(C_1 C_6) haloalcoxi(C_1 C_6) mono- y di- (C_1-C_6) alquilamino XR_C

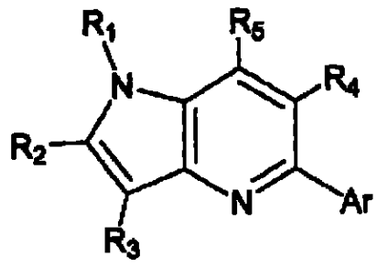
14 Un compuesto o sal de acuerdo con la Reivindicación 13 en donde

R_1 se selecciona de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales sustituido con de 0 a 2 sustituyentes independientemente seleccionados de

(i) halógeno hidroxi amino ciano o

(ii) alquilo C_1 C_4 alcoxi C_1 C_4 y mono- y di (C_1 C_4) alquilamino cada uno de los cuales sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-9}

15 Un compuesto o sal de acuerdo con la Reivindicación 3 de la Fórmula VIII



Fórmula VIII

en donde R_1 R_2 R_3 R_4 R_5 y Ar son definidos como en la Reivindicación 3

16 Un compuesto o sal de acuerdo con la Reivindicación 15 en donde

R_1 se define como la Reivindicación 3

R_2 se selecciona de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_3

R_4 y R_5 son independientemente seleccionados de hidrógeno halógeno ciano amino alquilo C_1-C_6 alcoxi C_1 C_6 cicloalquilo C_3-C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 (cicloalquilo C_3-C_7) alcoxi C_1-C_4 mono y di (alquilo C_1-C_6) amino amino(C_1-C_6) alquilo mono y di (alquilo C_1 C_6) amino (C C_6) alquilo halo (C_1 C_6) alquilo y halo (C_1 C_6)alcoxi y

Ar se selecciona del grupo que consiste de fenilo pirídilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1 C_6) halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1 C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3-C_7 (cicloalquilo C_3-C_7)alquilo C_1 C_4 alcoxi C_1 C_6 mono- y di (alquilo C_1 C_6)amino amino (C_1 C_6) alquilo y mono y di (alquilo C_1 C_6)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula VIII es sustituido

17 Un compuesto o sal de acuerdo con la Reivindicación 15 en donde

R_1 se selecciona de alquilo C_1 C_{10} y (cicloalquilo C_3-C_{10}) alquilo C_0-C_4 cada uno de los cuales sustituido con 0 o más sustituyentes seleccionados

independientemente de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono- y di (C_1 C_4) alquilamino

18 Un compuesto o sal de acuerdo con la Reivindicación 15 en donde

R_1 se selecciona de heterocicloalquilo C_{3-9} y (heterocicloalquilo C_{3-9}) alquilo C_1-C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1 C_6 alcoxi C_1-C_6 hidroxialquilo C_1 C_6 alcoxi C_1 C_6 alquilo C_1 C_6 haloalquilo(C_1-C_6) haloalcoxi(C_1 C_6) mono- y di (C_1-C_6) alquilamino XR_C

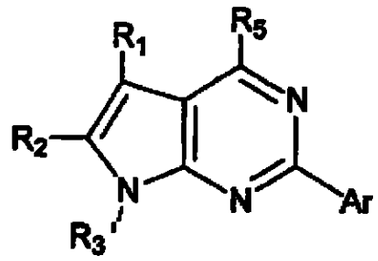
19 Un compuesto o sal de acuerdo con la Reivindicación 18 en donde

R_1 se selecciona de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales sustituido con de 0 a 2 sustituyentes independientemente seleccionados de

(i) halógeno hidroxi amino ciano o

(ii) alquilo C_1-C_4 alcoxi C_1-C_4 y mono y di (C_1 C_4) alquilamino cada uno de los cuales sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-9}

20 Un compuesto o sal de acuerdo con la Reivindicación 3 de la Fórmula X



Fórmula X

en donde R_1 R_2 R_3 R_5 y Ar son definidos como en la Reivindicación 3

21 Un compuesto o sal de acuerdo con la Reivindicación 20 en donde

R_1 se define como la Reivindicación 3

R_2 se selecciona de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_6

R_5 se selecciona de hidrógeno halógeno ciano amino alquilo C_1 C_6 alcoxi C_1 C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 (cicloalquilo C_3 C_7) alcoxi C_1 C_4 mono y di (alquilo C_1 C_6) amino amino(C_1-C_6) alquilo mono y di (alquilo C_1 C_6) amino (C-C_6) alquilo halo (C_1 C_6) alquilo y halo (C_1 C_6)alcoxi y

Ar se selecciona del grupo que consiste de fenilo piridilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1 C_6) halo (C_1 C_6) alcoxi hidroxi amino alquilo C_1-C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 alcoxi C_1 C_6 mono- y di (alquilo C_1-C_6)amino amino (C_1 C_6) alquilo y mono y di (alquilo C_1 C_6)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula X se sustituye

22 Un compuesto o sal de acuerdo con la Reivindicación 20 en donde

R_1 se selecciona de alquilo C_1 C_{10} y (cicloalquilo C_3-C_{10}) alquilo C_0-C_4 cada uno de los cuales sustituido con 0 o más sustituyentes seleccionados independientemente de halógeno hidroxi amino oxo ciano alcoxi C_1-C_4 y mono y di (C_1-C_4) alquilamino

23 Un compuesto o sal de acuerdo con la Reivindicación 23 en donde

R_1 se selecciona de heterocicloalquilo C_{3-9} y (heterocicloalquilo C_{3-9}) alquilo C_1 C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1-C_6 alcoxi C_1 C_6 hidroxialquilo C_1 C_6 alcoxi C_1 C_6 alquilo C_1 C_6 haloalquilo(C_1-C_6) haloalcoxi(C_1-C_6) mono- y di (C_1 C_6) alquilamino XR_C

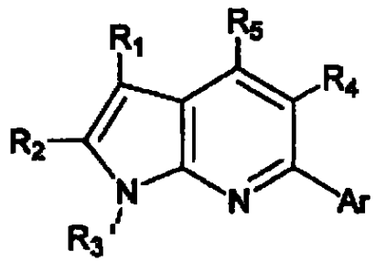
24 Un compuesto o sal de acuerdo con la Reivindicación 23 en donde

R_1 se selecciona de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales sustituido con de 0 a 2 sustituyentes independientemente seleccionados de

(i) halógeno hidroxi amino ciano o

(ii) alquilo C_1-C_4 alcoxi C_1 C_4 y mono- y di (C_1-C_4) alquilamino cada uno de los cuales sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-9}

25 Un compuesto o sal de acuerdo con la Reivindicación 3 de la Fórmula XII



Fórmula XII

en donde R_1 R_2 R_3 R_4 R_5 y Ar son definidos como en la Reivindicación 3

26 Un compuesto o sal de acuerdo con la Reivindicación 25 en donde

R_1 se define como la Reivindicación 3

R_2 se selecciona de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_6

R_4 y R_5 son independientemente seleccionados de hidrógeno halógeno ciano amino alquilo C_1-C_6 alcoxi C_1 C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 (cicloalquilo C_3-C_7) alcoxi C_1-C_4 mono y di (alquilo C_1-C_6) amino amino(C_1 C_6) alquilo mono y di (alquilo C_1-C_6) amino (C C_6) alquilo halo (C_1 C_6) alquilo y halo (C_1-C_6)alcoxi y

Ar se selecciona del grupo que consiste de fenilo pirídilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1

C_8) halo (C_1 C_6) alcoxi hidroxi amino alquilo C_1 C_8 alquenilo C_2-C_8 alquinilo C_2-C_8 cicloalquilo C_3-C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 alcoxi C_1-C_8 mono- y di (alquilo C_1 C_8)amino amino (C_1-C_8) alquilo y mono- y di (alquilo C_1 C_8)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula XII es sustituido

27 Un compuesto o sal de acuerdo con la Reivindicación 25 en donde

R_1 se selecciona de alquilo C_1 C_{10} y (cicloalquilo C_3-C_{10}) alquilo C_0-C_4 cada uno de los cuales sustituido con 0 o más sustituyentes seleccionados independientemente de halógeno hidroxi amino oxo ciano alcoxi C_1 C_4 y mono- y di- (C_1-C_4) alquilamino

28 Un compuesto o sal de acuerdo con la Reivindicación 25 en donde

R_1 se selecciona de heterocicloalquilo C_{3-8} y (heterocicloalquilo C_{3-8}) alquilo C_1 C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1 C_8 alcoxi C_1 C_8 hidroxialquilo C_1 C_8 alcoxi C_1 C_8 alquilo C_1 C_8 haloalquilo(C_1 C_8) haloalcoxi(C_1-C_8) mono- y di- (C_1 C_8) alquilamino XR_C

29 Un compuesto o sal de acuerdo con la Reivindicación 28 en donde

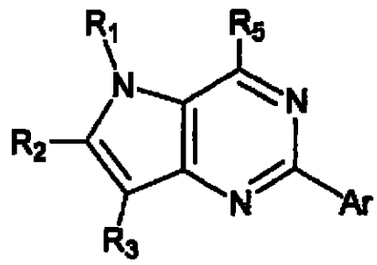
R_1 se selecciona de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales

sustituido con de 0 a 2 sustituyentes independientemente seleccionados de

(i) halógeno hidroxi amino ciano o

(ii) alquilo C_1-C_4 alcoxi C_1-C_4 y mono- y di- (C_1-C_4) alquilamino cada uno de los cuales sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-9}

30 Un compuesto o sal de acuerdo con la Reivindicación 3 de la Fórmula XIV



Fórmula XIV

en donde R_1 R_2 R_3, R_5 y Ar son definidos como en la Reivindicación 3

31 Un compuesto o sal de acuerdo con la Reivindicación 30 en donde

R_1 se define como la Reivindicación 3

R_2 se selecciona de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_3

R_5 se selecciona de hidrógeno halógeno ciano amino alquilo C_1 C_8 alcoxi C_1-C_8 cicloalquilo C_3 C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 (cicloalquilo C_3 C_7) alcoxi C_1 C_4 mono y di (alquilo C_1 C_8) amino amino(C_1-C_8) alquilo mono y di (alquilo C_1 C_8) amino (C-C_8) alquilo halo (C_1 C_8) alquilo y halo (C_1 C_8)alcoxi y

Ar se selecciona del grupo que consiste de fenilo piridilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1 C_6) halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1 C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3-C_7 (cicloalquilo C_3 C_7)alquilo C_1 C_4 alcoxi C_1 C_6 mono- y di (alquilo C_1-C_6)amino amino (C_1 C_6) alquilo y mono y di (alquilo C_1 C_6)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula XIV es sustituido

32 Un compuesto o sal de acuerdo con la Reivindicación 30 en donde

R_1 se selecciona de alquilo C_1 C_{10} y (cicloalquilo C_3-C_{10}) alquilo C_0-C_4 cada uno de los cuales sustituido con 0 o más sustituyentes seleccionados independientemente de halógeno hidroxi amino oxo ciano alcoxi C_1 C_4 y mono- y di (C_1 C_4) alquilamino

33 Un compuesto o sal de acuerdo con la Reivindicación 30 en donde

R_1 se selecciona de heterocicloalquilo C_{3-9} y (heterocicloalquilo C_{3-9}) alquilo C_1-C_4 cada uno de los cuales sustituido con 0-4 sustituyentes seleccionados de halógeno amino hidroxi nitro ciano alquilo C_1 C_6 alcoxi C_1 C_6 hidroxialquilo C_1-C_6 alcoxi C_1 C_6 alquilo C_1-C_6 haloalquilo(C_1 C_6) haloalcoxi(C_1-C_6) mono y di (C_1 C_6) alquilamino XR_C

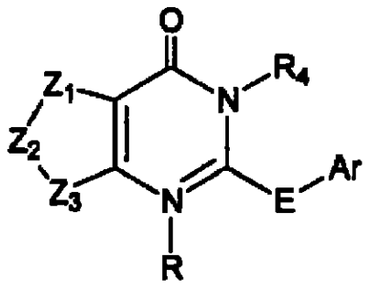
34 Un compuesto o sal de acuerdo con la Reivindicación 33 en donde

R_1 se selecciona de tetrahidrofuranilo tetrahidropiranilo morfolinilo pirrolidinilo piperidinilo anillos azabicíclicos piperazinilo [2 2 1] anillos azabicíclicos [2 2 2] anillos azabicíclicos [3 3 1] quinuclidinilo azetidinilo azetidinonilo oxindolilo dihidroimidazolilo y pirrolidinonilo cada uno de los cuales sustituido con de 0 a 2 sustituyentes independientemente seleccionados de

(i) halógeno hidroxi amino ciano o

(ii) alquilo C_1 C_4 alcoxi C_1 C_4 y mono- y di (C_1 C_4) alquilamino cada uno de los cuales sustituido con 0 o 1 sustituyentes seleccionados de halógeno hidroxi amino alcoxi C_{1-2} o heterocicloalquilo C_{3-8}

35 Un compuesto o sal de acuerdo con la Reivindicación 3 de la Fórmula XX



Fórmula XX

o una sal farmacéuticamente aceptable de esta en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1 C_4

m es 0 1 o 2

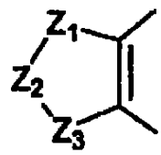
Ar se escoge de

fenilo que es mono- di- o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono di o tri-sustituido y opcionalmente

heteroarilo mono- di o tri-sustituido dicho heteroarilo que tiene de 1 a aproximadamente 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionados del grupo que consiste de N O y S

R es oxígeno o está ausente

el grupo



representa un sistema de anillo de 5 miembros saturado insaturado o aromático que contiene 0 o 1 heteroátomos en donde

Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 CR_3R_3 o NR3

R_1 se escoge de halógeno hidroxi ciano amino alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido alcoxi opcionalmente sustituido mono o di alquilamino opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido cicloalquilo opcionalmente sustituido heterocicloalquilo opcionalmente sustituido alquiltio opcionalmente sustituido alquilsulfinilo opcionalmente sustituido alquilsulfonilo opcionalmente sustituido mono-o di alquilcarboxamida opcionalmente sustituido anlo carbocíclico opcionalmente sustituido y heteroarilo opcionalmente sustituido dicho heteroarilo opcionalmente sustituido tiene de 1 a 3 anillos 5 a 7 miembros

de anillo en cada anillo y en al menos uno de dichos anillos de 1 a aproximadamente 3 heteroátomos seleccionados del grupo que consiste de N O y S

R1 se escoge de alquilo opcionalmente sustituido alquenilo opcionalmente sustituido alquinilo opcionalmente sustituido (cicloalquil) alquilo opcionalmente sustituido cicloalquilo opcionalmente sustituido heterocicloalquilo opcionalmente sustituido (heterocicloalquil) alquilo opcionalmente sustituido arilo carbocíclico opcionalmente sustituido y heteroarilo opcionalmente sustituido dicho heteroarilo opcionalmente sustituido tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a 3 heteroátomos seleccionados del grupo que consiste de N O y S

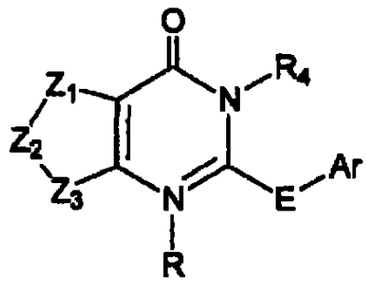
R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo haloalquilo alcoxi aminoalquilo y mono y dialquilamino

R R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo haloalquilo y aminoalquilo

R_2 y R_3 son independientemente escogidos de hidrógeno alquilo haloalquilo y aminoalquilo y

R_4 es hidrógeno alquilo aminoalquilo y haloalquilo

36 Un compuesto de la fórmula



o una sal farmacéuticamente aceptable de esta en donde

E es un enlace simple O $S(O)_m$ NR_{10} o $CR_{10}R_{11}$

R_{10} y R_{11} son independientemente hidrógeno o alquilo C_1 C_4

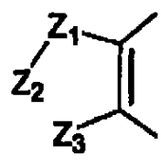
m es 0 1 o 2

R es oxígeno o está ausente

Ar se escoge de

fenilo que es mono di o tri-sustituido 1 naftilo y 2 naftilo cada uno de los cuales es opcionalmente mono- di- o tri-sustituido y opcionalmente heteroarilo mono- di o tri-sustituido dicho heteroarilo que tiene de 1 a 3 anillos 5 a 7 miembros de anillo en cada anillo y en al menos uno de dichos anillos de 1 a 3 heteroátomos seleccionados del grupo que consiste de N O y S

el grupo



representa un sistema de anillo saturado insaturado o aromático que contiene 0 o 1 heteroátomos en donde

Z_1 es CR_1 CR_1R_1 o NR_1

Z_2 es nitrógeno oxígeno azufre CR_2 CR_2R_2 o NR_2

Z_3 es nitrógeno oxígeno azufre sulfóxido sulfona CR_3 CR_3R_3 o NR3

R_1 se escoge de

i) halógeno hidroxi ciano amino carbhidrilo C_1 C_{10} -O(carbhidrilo C_1-C_8) mono o di (carbhidrilo C_1-C_8)amino (ciclocarbhidrilo C_3 C_7) carbhidrilo C_1 C_4 halo (C_1 C_8) carbhidrilo O(halo (C_1-C_8) carbhidrilo) y S(O) (carbhidrilo C_1 C_8) -O(ciclocarbhidrilo C_3 C_7) carbhidrilo C_1 C_4 heterociclоalquilo C_{3-9} (heterociclоalquilo C_{3-9}) alquilo C_1 C_4 y S(O) (carbhidrilo C_1 C_8)

donde cada carbhidrilo es independientemente recto ramificado o cíclico contiene cero o 1 o más dobles o triple enlaces

donde cada heterociclоalquilo tiene 1 o 2 heteroátomos en el anillo seleccionados de N O o S y el punto de unión es carbono o nitrógeno y

donde cada carbhidrilo heterociclоalquilo o ciclocarbhidrilo es opcionalmente sustituido por uno o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1-C_8 alcoxi C_1 C_8 haloalcoxi C_1-C_8 alcanoilo C_1 C_8 alcanoiloxi C_1 C_8 alcoxicarbonilo C_1 C_8 N (alcanoilo C_1-C_8) N (alquilo C_0-C_8)amino N (alcanoiloxi C_1 C_8) N (alquilo C_0-C_8)amino N-(alcoxicarbonilo C_1-C_8) N (alquilo C_0-C_8)amino alquilsulfonamida C1 C_8 alquilosulfonilo C_1 C_8 alquilosulfoniloxi C_1-C_8 hidroxialquilo C_1 C_8 alcoxi C_1 C_8 alquilo C_1 C_8 haloalcoxi C_1 C_8 heteroarilo de 5 a 7 miembros heterociclоalquilo de 5 a 7 miembros mono- y di- (C_1-C_8) alquilamino N (alcanoilo C_1-C_8) N (alquil C_0-C_8)amino

N (alcanoiloxi C_1 C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1 C_6) N (alquil C_0-C_6) amino mono- y di (C_1-C_6) alquilcarbamoilo XR_C y X Z y

ii) fenilo que es mono- di o tri-sustituido con R_A 1 naftilo 2 naftilo piridilo dihidropiridilo tetrahidropiridilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales es opcionalmente mono- di o tri-sustituido con R_A

R_1 se escoge de alquiloC_1-C_{10} alquenilo C_2-C_{10} alquinilo C_2-C_{10} cicloalquilo C_3 C_7 (cicloalquilo C_3-C_7) alquilo C_1 C_4 heterocicloalquilo C_{3-9} (heterocicloalquilo C_{3-9}) alquilo C_1 C_4 y halo (C_1 C_6) alquilo cada uno de los cuales es sustituido con 0 o más sustituyentes independientemente escogidos de halógeno hidroxi amino oxo ciano alquilo C_1 C_6 alcoxi C_1 C_6 haloalcoxi C_1 C_6 alcanoilo C_1-C_6 alcanoiloxi C_1 C_6 alcoxicarbonilo C_1 C_6 N (alcanoilo C_1 C_6) N (alquil C_0-C_6) amino N (alcanoiloxi C_1 C_6) N (alquil C_0-C_6) amino N (alcoxicarbonilo C_1 C_6) N (alquilo C_0-C_6) amino alquilo sulfonamida C_1 C_6 alquilsulfonilo C_1 C_6 alquilsulfoniloxi C_1-C_6 hidroxialquilo C_1 C_6 alcoxi C_1-C_6 alquilo C_1 C_6 haloalcoxi C_1-C_6 heteroarilo de 5 a 7 miembros heterocicloalquilo de 5 a 7 miembros mono y di (C_1-C_6) alquilamino N (alcanoilo C_1 C_6) N (alquilO C_0-C_6) amino N (alcanoiloxi C_1 C_6) N (alquilo C_0 C_6) amino N (alcoxicarbonilo C_1 C_6) N (alquilo C_0-C_6) amino mono- y di alquilcarbamoilo (C_1 C_6) XRc y X Z

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno hidroxi amino ciano nitro alquilo C_1-C_6 halo (C_1 C_6) alquilo alcoxi C_1 C_6 amino (C_1 C_6) alquilo y mono y di (C_1 C_6) alquilamino

R_2 y R_3 son independientemente escogidos de hidrógeno halógeno alquilo C_1-C_6 halo (C_1 C_6) alquilo y amino (C_1-C_6) alquilo

R_2 y R_3 son independientemente escogidos de hidrógeno alquilo C_1 C_6o halo (C_1 C_6) alquilo y amino (C_1 C_6) alquilo

R_4 es hidrógeno alquilo C_1 C_6 aminoalquilo C_1 C_6 y haloalquilo C_1-C_6

R_A es independientemente seleccionado en cada ocurrencia de halógeno ciano nitro halo (C_1 C_6) alquilo halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1-C_6 sustituido con 0-2 R_B alquenilo C_2-C_6 sustituido con 0 2 R_B alquinilo C_2-C_6 sustituido con 0 2 R_B cicloalquilo C_3-C_7 sustituido con 0 2 R_B (cicloalquilo C_3-C_7) alquilo C_1-C_4 sustituido con 0 2 R_B alcoxi C_1-C_6 sustituido con 0 2 R_B NH(alquilo C_1-C_6) sustituido con 0 2 R_B N(alquilo C_1 C_6)(alquilo C_1-C_6) cada alquilo C_1 C_6 independientemente sustituido con 0 2 R_B XRc y Y

R_B es independientemente seleccionado en cada ocurrencia del grupo que consiste de halógeno hidroxi ciano amino alquilo C_1-C_4 O(alquilo C_1 C_4) NH(Cz C_4alquilo) N(alquilo C_1 C_4)(alquilo C_1 C_4) S(O) (alquilo) halo (C_1-C_4) alquilo halo (C_1-C_4) alcoxi CO(alquilo C_1 C_4) CONH(alquilo C_1 C_4) CON(alquilo C_1-C_4)(alquilo C_1-C_4) XR_C y Y

R_C y R_D que pueden ser iguales o diferentes son independientemente seleccionados en cada ocurrencia de

hidrógeno y

grupos alquilo rectos ramificados o cíclicos que incluyengrupos (cicloalquil) alquilo que consisten de 1 a 8 átomos de carbono cuyos grupos alquilo rectos ramificados o cíclicos contiene cero o uno o más dobles o triples enlaces cada uno de los cuales 1 a 8 átomos de carbono pueden ser adicionalmente sustituido con uno o más sustituyente o sustituyentes independientemente seleccionados de oxo hidroxi halógeno ciano amino alcoxi C_1-C_8 NH(alquilo C_1 C_8) N(alquilo C_1 C_8)(alquilo C_1 C_8) NHC(=O)(alquilo C_1 C_8) N(alquilo C_1 C_8)C(=O)(alquilo C_1 C_8) NHS(O) (alquilo C_1 C_8) S(O) (alquilo C_1-C_8) S(O) NH(alquilo C_1 C_8) S(O) N(alquilo C_1 C_8)(alquil C_1-C_8) y Z

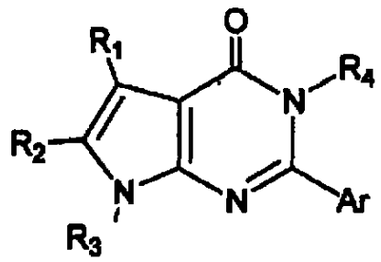
X es independientemente seleccionado en cada ocurrencia del grupo que consiste de CH2 -CHRD -0- C(=O) -C(=O)O S(O) NH NR_D- C(=O)NH C(=O)NR_D- -S(O) NH S(O) NR_D- -OC(=S)S NHC(=O) NR_DC(=O)- $NHS(O)_n$- $-OSiH_2$- OSiH(alquilo C_1-C_4) OSi(alquilo C_1-C_4) (alquilo C_1 C_4) y NR_DS(O)

Y y Z son independientemente seleccionado en cada ocurrencia de grupos carbocíclicos y heterocíclicos de 3 a 7 miembros que son saturados insaturados o aromáticos que pueden ser adicionalmente sustituidos con uno o más sustituyentes independientemente seleccionados de halógeno oxo hidroxi amino ciano alquilo C_1 C_4 O(alquilo C_1-C_4) -C(O)(alquilo C_1 C_4) NH(alquilo C_1 C_4) N(alquilo C_1 C_4)(alquilo C_1 C_4) yS(O) (alquilo)

en donde dichos grupos heterocíclicos de 3 a 7 miembros contienen uno o más heteroátomo o heteroátomos independientemente seleccionados de N O y S con el punto de unión siendo carbono o nitrógeno y

n es independientemente seleccionado en cada ocurrencia de 0 1 y 2

37 Un compuesto o al de acuerdo a la reivindicación 36 de la Fórmula XXI



Fórmula XXI

en donde

R_1 R_2 R_3 R_4 son definidos como en la Reivindicación 37 y

Ar se escoge de

fenilo que es mono- di o tri-sustituido con R_A y 1 naftilo 2 naftilo pirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono- di o tri-sustituido con R_A

38 Un compuesto o sal de acuerdo con la Reivindicación 37 en donde

R_1 se define como la Reivindicación 36

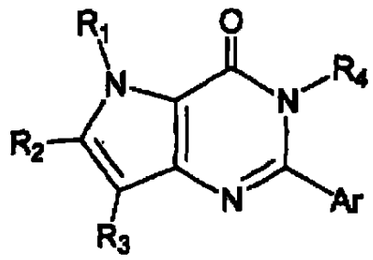
R_2 y R_4 se seleccionan independientemente de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_6 y

Ar se selecciona del grupo que consiste de fenilo pirídilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1

C_6) halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1-C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3 C_7 (cicloalquilo C_3-C_7)alquilo C_1-C_4 alcoxi C_1 C_6 mono y di (alquilo C_1-C_6)amino amino (C_1 C_6) alquilo y mono y di (alquilo C_1-C_6)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula XXI es sustituido

39 Un compuesto o sal de acuerdo con la Reivindicación 36 de la Fórmula XXII



Fórmula XXII

en donde R_1 R_2 R_3 R_4 y R_5 son definidos como en la Reivindicación 36 y

Ar se escoge de

fenilo que es mono di o tri-sustituido con R_A y 1 naftilo 2 naftilo pirídilo pirimidinilo pirazinilo piridizinilo tienilo tiazolilo oxazolilo isoxazolilo pirrolilo furanilo y triazolilo cada uno de los cuales opcionalmente mono- di o tri-sustituido con R_A

40 Un compuesto o sal de acuerdo con la Reivindicación 39 en donde

R_1 se define como la Reivindicación 39

R_2 y R_4 se seleccionan independientemente de hidrógeno metilo y etilo

R_3 es hidrógeno o alquilo C_1C_6 y

Ar se selecciona del grupo que consiste de fenilo pirídilo y pirimidinilo cada uno de los cuales es mono-di-o trisustituido con sustituyentes independientemente escogidos de halógeno ciano nitro halo (alquilo C_1 C_6) halo (C_1-C_6) alcoxi hidroxi amino alquilo C_1 C_6 alquenilo C_2-C_6 alquinilo C_2-C_6 cicloalquilo C_3-C_7 (cicloalquilo C_3-C_7)alquilo C_1 C_4 alcoxi C_1 C_6 mono- y di (alquilo C_1 C_6)amino amino (C_1 C_6) alquilo y mono y di (alquilo C_1 C_6)amino en donde en Ar al menos una de las posiciones orto de el punto de unión de Ar mostrado en la Fórmula XXII es sustituido

41 Un compuesto o sal farmacéuticamente aceptable de este en donde el compuesto se selecciona del grupo que consiste de

5-(1 Etil propil) 2 (2 metoxi-4 trifluorometoxi fenil) 3 7-dimetil 5H pirrolo[2 3-b]pirazina

{4-Etil 5 [5 (1-etil propil) 3 7-dimetil-5H pirrolo[2 3 b]pirazin 2 il]-piridin 2 il}-dimetil-amina

{3 Bromo-4-etil 5 [5-(1-etil propil)-3 7-dimetil-5H pirrolo[2 3 b]pirazin 2 il] piridin 2 il}-etil metil amina

Etil-4-{etil 5 [5-(1-etil-propil) 3 7-dimetil 5H pirrolo[2 3-b]pirazin 2 il] piridin 2 il}-metil-amina

{5-[5 (1 Etil propil) 3 7-dimetil 5H-pirrolo[2 3-b]pirazin 2 il]-4 metoxi piridin 2 il}-dimetil amina

2 [2 Etoxi 5 metanosulfonil-6-(1 metil but 3-enil) piridin 3 il] 5 (1-etil propil) 3 7 dimetil 5H pirrolo[2 3 b]pirazina

2 (2 Etoxi-6-etil 5-metanosulfonil piridin 3 il)-5-(1-etil propil) 3 7-dimetil 5H pirrolo[2 3-b]pirazina

{5-[3-Cloro-5 (1-etil propil) 7 metil 5H pirrolo[2 3 b]pirazin 2 il]-4-etil piridin 2 il) etil metil-amina

{5 [3-Cloro-5 (1-etil propil)-7 metil 5H pirrolo[2 3-b]pirazin 2 il]-4-etil piridin 2 il}-dimetil-amina

{5-[3 Cloro 5-(1-etil propil) 7 metil 5H pirrolo[2 3-b]pirazin 2 il]-4-etil piridin 2 il}-dietil-amina

3 Cloro-5 (1-etil propil) 2 (3 isopropil 5 metoxi 2 3-dihidro furo[3 2 b]piridin-6 il) 7 metil-5H-pirrolo[2 3-b]pirazina

3 Cloro-5 (1-etil propil) 2 (3 isopropil 5-metoxi-furo[3 2 b]piridin-6-il) 7 metil 5H pirrolo[2 3 b]pirazina

(R) 2 [2 (6 Isopropil 2 metoxi-piridin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5-il] 3 metoxi-propan 1-ol

5-(1 Etil propil) 2 (6 isopropil 2 metoxi piridin-3 il) 3 7-dimetil-5H pirrolo[2 3-b]pirazina

2 (2 Etil-6-isopropil-piridin 3 il) 5-(1-etil-propil) 3 7-dimetil 5H-pirrolo[2 3 b]pirazina

2 [(S) 2 (6-Isopropil 2 metoxi piridin 3 il)-3 7-dimetil pirrolo[2 3 b]pirazin 5-il] butano1ol

Ésterde2 [(S) 2 (6 isopropil 2 metoxi piridin 3-il) 3 7-dimetil-pirrolo[2 3 b]pirazin 5-il] butilodeácidometanosulfónico

3-{2 [(S)-2 (6 Isopropil 2 metoxi piridin 3 il)-3 7-dimetil pirrolo[2 3-b]pirazin-5-il] butil}-oxazolidin 2-ona

(S) 2 (6-Isopropil 2 metoxi-piridin-3 il) 5-(1 metoximetil propil) 3 7-dimetil 5H pirrolo[2 3-b]pirazina

Etil-{2 [(S) 2-(6-isopropil 2 metoxi piridin-3-il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-metil-amina

{2 [(S) 2 (6-Isopropil 2 metoxi-piridin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5-il] butil}-metil amina

N-{2 [(S) 2 (6-Isopropil 2 metoxi piridin 3-il) 3 7-dimetil pirrolo[2 3 b]pirazin 5-il]-butil}-N metil metanesulfonamida

N-{2-[(S) 2 (6 Isopropil 2-metoxi piridin 3-il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil N metil acetamida

Ésterdemetilodeácido{2 [(S) 2 (6 Isopropil 2 metoxi-piridin-3-il) 3 7-dimetil-pirrolo[2 3 b]pirazin 5 il] butil}-metil carbámico

(R) 2 (6-Isopropil 2 metoxi pindin 3 il)-5-(1 metoximetil propil) 3 7-dimetil-5H pirrolo[2 3 b]pirazina

Ésterde2 [(R) 2 (6 isopropil 2 metoxi piridin 3-il) 3 7-dimetil-pirrolo[2 3 b]pirazin 5 il] butilodeácidoacético

2 [(R) 2 (6 Isopropil 2 metoxi-piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butan1ol

(R)-2 (2 Etil-6 isopropil piridin 3 il) 5 (1 metoximetil propil) 3 7-dimetil 5H pirrolo[2 3 b]pirazina

{6 Isopropil 3-[(R)-5-(1 metoximetil propil) 3 7-dimetil 5H pirrolo[2 3-b]pirazin 2 il] piridin 2 il}-metil amina

{2 [(R) 2 (6 Isopropil 2 metoxi pindin 3-il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil}-dimetil-amina

(R) 2 (6-Isopropil 2 metoxi piridin 3 il) 3 7-dimetil 5-(1 pirrolidin 1 ilmetil propil) 5H pirrolo[2 3 b]pirazina

Dietil-{2-[(R) 2 (6 isopropil 2 metoxi pindin 3 il) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil3-amina

Isopropil-{2 [(R) 2 (6-isopropil 2 metoxi pindin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-metil amina

(R)-2 (6 Isopropil 2 metoxi-piridin 3 il) 3 7-dimetil 5-(1-morfolin-4 ilmetil propil) 5H pirrolo[2 3-b]pirazina

Ciclobutil-{ [(R) 2 (6-isopropil 2-metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-amina

{2-[(R) 2 (6 Isopropil-2-metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin-5 il] butil}-(2 metoxi-etil) metil amina

2 (6 Isopropil 2 metoxi piridin-3 il) 3 7-dimetil 5-(1 metileno-propil) 5H pirrolo[2 3-b]pirazina

Butil-etil-{2 [(R) 2 (6 isopropil 2 metoxi piridin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il] butil}-amina

5-sec-Butil 2 (6 isopropil 2 metoxi pindin 3 il)-3 7-dimetil 5H pirrolo[2 3 b]pirazina

Ésterde2 [(R)-2-(6-isopropil 2 metoxi-pindin 3 il) 3 7-dimetil-pirrolo[2 3 b]pirazin 5-il] butilodeácidodimetil-carbámico

{2 [(R) 2 (6 Isopropil 2 metoxi pindin-3 il)-3 7-dimetil pirrolo[2 3 b]pirazin 5-il] butil)-dipropil-amina

2 (6-Isopropil 2 metoxi pindin 3 il) 3 7-dimetil 5 [(R) 1 (4-metil piperazin 1 ilmetil) propil] 5H pirrolo[2 3-b]pirazina

1 (4-{(R) 2 [2 (6 Isopropil 2 metoxi-pindin 3 il) 3 7-dimetil pirrolo[2 3-b]pirazin 5 il]-butil}-piperazin 1 il)-etanona

2 (2 Etil-6 isopropil pindin 3 il) 3 7-dimetil 5 ((R) 1 morfolin-4-ilmetil propil) 5H pirrolo[2 3 b]pirazina

{3 [3 7 Dimetil 5 ((R) 1 morfolin-4 ilmetil propil)-5H-pirrolo[2 3-b]pirazin 2 il]-6 isopropil pindin 2 il}-metil amina

{(R) 2 [2 (4 Difluorometoxi 2 metoxi fenil) 3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil}-etil metil-amina

{(R) 2 [2 (2 Cloro-4 metoxi fenil)-3 7-dimetil pirrolo[2 3 b]pirazin 5 il] butil}-etil metil-amina

5-Isopropil 2 (6-isopropil 2 metoxi piridin 3-il) 3 7-dimetil 5H pirrolo[2 3 b]pirazina

[6-Isopropil 3 (5 isopropil 3 7-dimetil 5H pirrolo[2 3 b]pirazin 2 il) piridin 2 il] metil amina

2 (2 Etil-6 isopropil piridin 3 il) 5-isopropil 3 7-dimetil 5H pirrolo[2 3 b]pirazina

2 (4 Difluorometoxi 2 metoxi fenil) 5-isopropil 3 7-dimetil 5H pirrolo[2 3 b]pirazina

5 Isopropil 2 (2 metoxi-4 trifluorometil fenil) 3 7-dimetil 5H pirrolo[2 3 b]pirazina

[3 (3 7 Dimetil-5-propil 5H pirrolo[2 3 b]pirazin 2 il)-6 isopropil piridin 2 il]-metil amina

2 (6-Isopropil-2-metoxi-piridin 3 il) 3 7-dimetil 5 propil 5H pirrolo[2 3 b]pirazina

5 Isopropil 2 (2 metoxi-4 trifluorometoxi fenil) 3 7-dimetil 5H pirrolo[2 3 b]pirazina 2 (2 Etil-6-isopropil piridin 3 il) 3 7-dimetil 5 propil 5H pirrolo[2 3 b]pirazina

(R) 2 (6 Isopropil piridin 3 il) 5 (1 metoximetil propil) 3 7-dimetil 5H pirrolo[2 3 b]pirazina

(S) 2 (2 Etil-6-isopropil piridin 3-il) 5 (1 metoximetil-propil) 3 7-dimetil-5H pirrolo[2 3 b]pirazina

{6 Isopropil 3 [(S) 5 (1 metoximetil propil) 3 7-dimetil 5H pirrolo[2 3-b]pirazin 2 il] piridin 2 il}-metil-amina

(S) 3-Cloro-2 (6 isopropil 2-metoxi piridin-3 il) 5 (2 metoxi 1 metil-etil)-7 metil-5H-pirrolo[2 3 b]pirazina

(S) 3 Etil 2 (6 isopropil 2 metoxi piridin 3 il)-5 (2 metoxi 1 metil-etil) 7 metil 5H pirrolo[2 3 b]pirazina

{3 [3 Etil 5-((S) 2 metoxi 1-metil-etil) 7 metil-5H pirrolo[2 3 b]pirazin 2 il]-6-isopropil-piridin 2 il}-metil-amina

{3-[3-Cloro-5 ((S) 2 metoxı 1 metıl-etıl) 7-metıl 5H pırrolo[2 3-b]pırazın 2 ıl]-6-ısopropıl-pırıdın 2 ıl}-metıl-amına

{6-Isopropıl-3-[5-((R) 1 metoxımetıl-propıl)-3 7-dımetıl 5H pırrolo[2 3 b]pırazın 2 ıl]-pırıdın 2 ıl}-dımetıl amına

3 Cloro-2 (6-ısopropıl 2 metıl pırıdın 3-ıl) 5 ((S) 2 metoxı 1 metıl-etıl) 7 metıl 5H pırrolo[2 3 b]pırazına

5-((R) 1 Etoxımetıl-propıl) 2 (6-ısopropıl 2 metoxı pırıdın 3 ıl) 3 7-dımetıl 5H pırrolo[2 3 b]pırazına

2-(6 Isopropıl 2-metıl pırıdın 3 ıl) 5 ((R) 1 metoxımetıl propıl)-3 7-dımetıl 5H pırrolo[2 3 b]pırazına

{3-[5 ((R) 1 Etoxımetıl propıl) 3 7-dımetıl-5H pırrolo[2 3-b]pırazın 2 ıl]-6-ısopropıl pırıdın 2–ıl}-metıl-amına

Etıl-{6 ısopropıl-3-[5 ((R) 1 metoxımetıl propıl) 3 7-dımetıl 5H pırrolo[2 3 b]pırazın 2 ıl] pırıdın 2 ıl}-amına

1 (1 Etıl propıl) 5 (2 metoxı-4 trıfluorometoxı fenıl) 3 6-dımetıl-1H pırrolo[3 2 b]pırıdına

Etıl-{4-etıl-5-[1 (1-etıl-propıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdın 5 ıl] pırıdın 2 ıl}-metıl amına

1 (1 Etıl propıl) 5 (6 ısopropıl 2 metoxı pırıdın 3 ıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

5 (2 Etıl-6 ısopropıl pırıdın 3 ıl)-1 (1-etıl propıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına {4 Etıl-5-[1 (1-etıl propıl)-3 6-dımetıl 1H pırrolo[3 2 b]pırıdın 5 ıl] pırıdın 2 ıl}-dımetıl amına

{3-[1 (1 Etıl propıl) 3 6-dımetıl 1H pırrolo[3 2-b]pırıdın-5-ıl]-6 ısopropıl pırıdın 2 ıl}-metıl-amına

1-sec-Butıl 5 (2 metoxı-4-trıfluorometoxı fenıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

1-sec-Butil 5 (6 isopropil 2 metoxi piridin-3-il) 3 6-dimetil 1H pirrolo[3 2 b]piridina 1 (2 Metoxi 1 metil-etil) 5-(2 metoxi-4 trifluorometoxi fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin 3 il) 1 (2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

1-sec-Butil 5 (2-etil-6 isopropil piridin 3-il) 3 6-dimetil-1H pirrolo[3 2 b]piridina

[3-(1-sec-Butil 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il)-6 isopropil piridin 2 il] metil-amina

5-(2 Etil-6 isopropil piridin 3-il) 1 (2 metoxi-1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{6 Isopropil 3 [1 (2 metoxi-1 metil-etil) 3 6-dimetil-1H-pirrolo[3 2 b]piridin 5 il] piridin 2 il}-metil-amina

1 Isopropil 5 (2 metoxi-4-trifluorometoxi-fenil)-3 6-dimetil-1H pirrolo[3 2 b]piridina 1 Isopropil-5-(6-isopropil 2 metoxi piridin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridina [6-Isopropil-3-(1 isopropil 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il) piridin 2 il] metil-amina

5 (2 Etil-6-isopropil piridin 3 il) 1 isopropil 3 6-dimetil-1H pirrolo[3 2 b]piridina

1-sec-Butil-6-etil 5 (6 isopropil 2 metoxi piridin 3 il)-3-metil 1H pirrolo[3 2 b]piridina

1 (2 Fluoro-etil) 5 (6 isopropil 2 metoxi-piridin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

1 [5-(6 Isopropil 2 metoxi piridin 3-il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] etanona Ésterdeetilodeácido[5 (6 Isopropil 2 metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il]-acético

1 Etil 5-(6 isopropil 2 metoxi piridin-3-il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

Ésterdeetilodeácido2 [5 (6 Isopropil 2 metoxi piridin-3-il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] propionico

5 (6-Isopropil 2 metoxi pirdin 3 il) 1 3 6-trimetil 1H pirrolo[3 2 b]piridina

5 (6-Isopropil 2 metoxi-piridin 3 il) 1 (2 metoxi-etil)-3 6-dimetil 1H-pirrolo[3 2 b]piridina

Ésterdeterc-butilo2-[5 (6 Isopropil 2-metoxi piridin 3-il)-3 6-dimetil pirrolo[3 2 b]pirdin 1 il] propionico

1 Etil-5 (2-etil-6-isopropil pirdin 3 il) 3 6-dimetil-1H pirrolo[3 2-b]piridina

[3-(1 Etil 3 6-dimetil 1H-pirrolo[3 2 b]piridin 5-il)-6 isopropil piridin 2 il] metil amina 5 (6 Isopropil 2 metoxi pirdin-3 il) 3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridina

1 (2 Etoxi-etil) 5 (6 isopropil 2 metoxi pirdin 3 il)-3 6-dimetil 1H pirrolo[3 2 piridina 5-(2 Etil-6-isopropil pirdin-3 il) 1 (2 fluoro-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina {3-[1 (2 Fluoro-etil) 3 6-dimetil 1H pirrolo[3 2-b]pirdin 5-il]-6 isopropil pirdin 2 il}-metil-amina

2 [5 (6 Isopropil 2 metoxi pirdin 3-il) 3 6-dimetil pirrolo[3 2 b]pirdin 1 il]-etanol

2 [5 (6-Isopropil 2 metoxi-piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il]-N metil-propionamida

5 (2 Etil-6 isopropil pirdin 3 il)-3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridina

1 Isobutil 5 (6 isopropil 2 metoxi pirdin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]pirdina

1-Ciclopropilmetil 5-(6-isopropil 2-metoxi pirdin-3-il) 3 6-dimetil 1H pirrolo[3 2 b]pirdina

Etil-[6-isopropil 3 (1 isopropil 3 6-dimetil 1H pirrolo[3 2 b]pirdin 5 il)-pirdin 2 il] amina

[3 (3 6-Dimetil 1 propil 1H-pirrolo[3 2 b]piridin 5-il)-6 isopropil-pirdin 2 il] metil amina

[3 (3 6 Dimetil 1 propil 1H pirrolo[3 2 b]piridin 5 il)-6 isopropil pirdin 2 il]-etil amina

1 (3 Fluoro-propil)-5-(6-isopropil 2 metoxi piridin 3 il) 3 6-dimetil 1H-pirrolo[3 2 b]piridina

1 [2 (2 Fluoro-etoxi)-etil]-5-(6-isopropil 2 metoxi piridin 3-il)-3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(2 Etil-6 isopropil piridin 3-il) 1 (3-fluoro-propil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{3-[1 (3-Fluoro-propil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 il}-metil-amina

5-(6 Isopropil 2 metoxi piridin 3 il) 1 (3 metoxi propil) 3 6-dimetil 1H-pirrolo[3 2 b]piridina

{6-Isopropil 3 [1 ((S) 2 metoxi 1-metil-etil)-3 6-dimetil-1H pirrolo[3 2 b]piridin 5-il] piridin 2 il}-metil-amina

5-(2 Etil-6-isopropil piridin 3 il) 1-((S) 2-metoxi 1 metil-etil) 3 6-dimetil-1H pirrolo[3 2 b]piridina

[3-(1 Isobutil 3 6-dimetil 1H pirrolo[3 2 b]piridin-5 il)-6 isopropil piridin 2 il] metil-amina

5-(2 Etil-6 isopropil piridin 3 il) 1 isobutil 3 6-dimetil 1H pirrolo[3 2 b]piridina

1 Butil-5 (6 isopropil 2 metoxi-piridin 3 il) 3 6-dimetil 1H-pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin 3 il) 3 6-dimetil 1 (2 morfolin-4 il-etil) 1H pirrolo[3 2 b]piridina

1-Allil 5 (6 isopropil 2 metoxi piridin 3 il)-3 6-dimetil 1H pirrolo[3 2 b]piridina

[3-(1 Butil-3 6-dimetil-1H pirrolo[3 2 b]piridin-5-il)-6-isopropil piridin 2 il] metil amina

1 Butil-5 (2-etil-6-isopropil piridin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

(R) 2 [5 (6 Isopropil 2 metoxi piridin 3 il)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] propan 1 ol

{6-Isopropil 3 [1-((R) 2 metoxi 1-metil-etil) 3 6-dimetil 1H-pirrolo[3 2 b]piridin-5 il] piridin 2 il}-metil-amina

5 (2 Etil-6 isopropil-piridin 3 il) 1-((R) 2 metoxi 1 metil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin-3-il) 1 ((R) 2 metoxi 1 metil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridina

1 ((R) 2 Fluoro-1-metil-etil) 5-(6-isopropil 2-metoxi piridin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5 (6-Isopropil 2 metoxi piridin 3-il) 3 6-dimetil 1-(2 metil-alil) 1H pirrolo[3 2 b]piridina

[3 (1-Alil-3 6-dimetil 1H-pirrolo[3 2 b]piridin 5-il)-6 isopropil piridin 2 il] metil amina 1-Alil 5 (2-etil-6 isopropil piridin 3 il) 3 6-dimetil-1H pirrolo[3 2 b]piridina

5 (6-Isopropil piridin 3 il) 3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridina

(S)-2 [5 (6-Isopropil 2 metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] 3 metoxi-propan 1-ol

1 ((R) 1 Fluorometil 2 metoxi-etil) 5 (6-isopropil 2 metoxi-piridin 3-il) 3 6 dimetil 1H pirrolo[3 2 b]piridina

{3 [1-((R) 1 Fluorometil 2 metoxi-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-6-isopropil-piridin 2 il}-metil amina

5-(2 Etil-6-isopropil-piridin 3 il) 1 ((R) 1 fluorometil 2 metoxi-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

1 ((R)-1 Fluorometil 2 metoxi-etil) 5 (6 isopropil piridin 3-il) 3 6-dimetil 1H pirrolo[3 2-b]piridina

5-(6 Isopropil 2 metoxi piridin 3 il) 1 (1 metoximetil butil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{5 Bromo-6 ısopropıl 3 [1 ((S) 2 metoxı 1 metıl-etıl) 3 6-dımetıl-1H-pırrolo[3 2 b]pırıdın 5 ıl] pırıdın 2 ıl}-metıl-amına

{5 Etıl-6-ısopropıl-3-[1 ((S)-2 metoxı-1 metıl-etıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdın 5 ıl] pırıdın 2 ıl}-metıl amına

1-((S)-1 Fluorometıl propıl) 5-(6-ısopropıl 2 metoxı pırıdın 3-ıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

1 ((R) 1 Fluorometıl propıl) 5 (6-ısopropıl-2 metoxı pırıdın 3 ıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

{3 [1-((S) 1 Fluorometıl-propıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdın 5-ıl]-6-ısopropıl pırıdın 2 ıl}-metıl amına

(S) 3 [5-(6-Isopropıl-2 metoxı pırıdın 3 ıl) 3 6-dımetıl pırrolo[3 2 b]pırıdın 1 ıl]-4-metoxı butırontrılo

(R) 2-[5-(6 Isopropıl 2 metoxı pırıdın 3 ıl) 3 6-dımetıl pırrolo[3 2 b]pırıdın 1 ıl] pentan 1-ol

5-(6 Isopropıl 2 metoxı pırıdın-3 ıl) 1 ((R) 1 metoxımetıl butıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

1 ((R) 1 Fluorometıl butıl)-5-(6 ısopropıl 2-metoxı pırıdın-3-ıl)-3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

5-(6 Isopropıl 2 metoxı pırıdın 3 ıl)-1 (1 metoxımetıl vınıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

{6 Isopropıl 3 [1 ((R)-1-metoxımetıl butıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdın-5 ıl] pırıdın 2 ıl}-metıl-amına

5 (2 Etıl-6 ısopropıl pırıdın 3 ıl) 1 ((R) 1 metoxımetıl butıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

(S) 2 [6 Etıl 5 (6 ısopropıl-2 metoxı pırıdın 3-ıl)-3 metıl pırrolo[3 2-b]pırıdın 1 ıl] 3 metoxı propan 1 ol

6 Etil 1 ((R) 1 fluorometil 2-metoxi-etil) 5 (6 isopropil 2-metoxi-piridin 3 il)-3 metil 1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin 3-il) 1 (2 metoxi-1 metoximetil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(2 Etil-6 isopropil piridin 3-il) 1 ((S) 1 fluorometil propil) 3 6-dimetil-1H pirrolo[3 2-b]piridina

1 ((S)-1 Fluorometil-propil) 5-(6 isopropil piridin 3 il) 3 6-dimetil 1H-pirrolo[3 2 b]piridina

{6 Isopropil-3 [1 (2 metoxi 1 metoximetil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5-il]-piridin 2 il}-metil-amina

1 ((S) 1 Etoximetil-propil) 5 (6 isopropil-2 metoxi piridin-3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

(R) 2 [5 (6-Isopropil 2 metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] 3 metoxi-propan 1-ol

1-((S)-1 Fluorometil 2 metoxi-etil)-5 (6 isopropil 2 metoxi piridin 3 il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{3-[1 ((S)-1 Fluorometil 2-metoxi-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 il}-metil-amina

6 Etil 1 isopropil 5 (6 isopropil 2 metoxi piridin 3 il) 3 metil 1H pirrolo[3 2 b]piridina

[3 (6-Etil-1 isopropil-3-metil-1H pirrolo[3 2 b]piridin 5 il)-6 isopropil-piridin 2 il] metil-amina

6 Etil 5-(2-etil-6 isopropil piridin-3 il) 1 isopropil-3-metil 1H pirrolo[3 2 piridina

5-(2 Etil-6 isopropil piridin-3-il) 1 (2 metoxi 1 metoximetil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{3-[1 ((S) 1 Etoximetil propil)-3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 il}-metil-amina

2 5 Dietil-6-[1 (1-etil propil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5-il]-3-isopropil 3H imidazo[4 5 b]piridina

(S) 2 [5-(2 Metoxi-4-trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butan 1-ol

1 ((S) 1 Metoximetil propil) 5 (2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil 1H pirrolo[3 2 b]piridina

1 ((S) 1 Clorometil propil) 5 (2 metoxi-4-trifluorometoxi-fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

1 ((S) 2 Metoxi 1 metil-etil)-5-(2 metoxi-4-trifluorometoxi-fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(2 Metoxi-4 trifluorometoxi fenil) 3 6-dimetil-1H pirrolo[3 2 b]piridina

5-(2 Metoxi-4-trifluorometoxi fenil) 3 6-dimetil 1 ((S) 1 morfolin-4 ilmetil propil) 1H pirrolo[3 2 b]piridina

{(S)-2 [5 (2 Metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butil}-dimetil-amina

5 (2 Metoxi-4-trifluorometoxi-fenil) 3 6-dimetil 1 ((S) 1 pirrolidin 1 ilmetil-propil) 1H pirrolo[3 2-b]piridina

(S) 2 [5 (6 Isopropil 2 metoxi piridin-3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butan 1 ol

5-(6 Isopropil 2 metoxi piridin 3 il) 1 ((S) 1 metoximetil-propil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

Ésterde(S) 2-[5 (6 isopropil 2-metoxi piridin-3 il) 3 6-dimetil-pirrolo[3 2 b]piridin 1 il] butilodeácidometanosulfónico

{(S) 2 [5-(6 Isopropil 2 metoxi piridin 3-il) 3 6-dimetil-pirrolo[3 2 b]piridin 1 il] butil}-dimetil amina

Éster de 2 [5-(2 metoxi-4-trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido (2R 6S) 2 6-Dimetil morfolina-4-carboxílico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido Pipendino 1 carboxílico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido 4-Metil piperazin 1 carboxílico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de Azepan 1 carboxílico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil-pirrolo[3 2 b]piridin-1 il]-butilo de ácido 4-Acetil-piperazin 1-carboxílico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido Etil-metil-carbámico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido Dietil carbámico

Éster de (S)-2 [5-(2 metoxi-4 trifluorometoxi-fenil)-3 6-dimetil-pirrolo[3 2 b]piridin 1 il] butilo de ácido Etil (2 metoxi-etil) carbámico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido(2 Metoxi-etil) carbámico

Éster de (S) 2 [5-(2 metoxi-4 trifluorometoxi fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butilo de ácido Ciclopentil-carbámico

1 [(S) 1 ((2S 6R) 2 6-Dimetil morfolin-4-ilmetil) propil] 5 (2 metoxi-4-trifluorometoxi fenil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5 (2 Metoxi-4 trifluorometoxi fenil) 3 6-dimetil 1 ((S) 1 piperidin 1 ilmetil propil) 1H-pirrolo[3 2 b]piridina

1 ((S) 1 Metanosulfonilmetil propil) 5-(2 metoxi-4-trifluorometoxi fenil) 3 6 dimetil 1H pirrolo[3 2 b]piridina

5 (2 Metoxi-4 trifluorometoxi fenil) 3 6-dimetil 1 [(S) 1 (4 metil piperazin 1 ilmetil)-propil] 1H pirrolo[3 2 b]piridina

1 ((S) 1-Azepan 1 ilmetil-propil) 5 (2-metoxi-4 trifluorometoxi fenil) 3 6-dimetil 1H-pirrolo[3 2 b]piridina

Éster de (S) 2 [5 (2 metoxi-4-trifluorometoxi-fenil) 3 6-dimetil pirrolo[3 2 b]piridin 1 il]-butilo de ácido Metanosulfónico

5-(6 Isopropil 2 metoxi piridin 3 il) 3 6-dimetil 1 ((S) 1 morfolin-4-ilmetil propil) 1H pirrolo[3 2 b]piridina

{3-[3 6 Dimetil 1 ((S) 1 morfolin-4-ilmetil propil) 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 il}-metil-amina

5 (2 Etil-6 isopropil piridin 3 il) 3 6-dimetil 1 ((S) 1 morfolin-4 ilmetil propil) 1H pirrolo[3 2 b]piridina

1 [(S) 1 (3 3-Dimetil-piperidin 1 ilmetil) propil]-5-(2 metoxi-4-trifluorometoxi-fenil) 3 6-dimetil-1H pirrolo[3 2-b]piridina

5-(2 Metoxi-4-trifluorometoxi fenil) 3 6-dimetil 1 ((S) 1 tiomorfolin-4 ilmetil propil) 1H pirrolo[3 2 b]piridina

1 [(S) 1 (4 4 Difluoro-piperidin 1 ilmetil) propil] 5-(2 metoxi-4 trifluorometoxi fenil)-3 6-dimetil 1H pirrolo[3 2-b]piridina

(R)-2 [5 (6-Isopropil 2 metoxi-piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butan 1-ol

5 (6 Isopropil 2 metoxi piridin 3-il) 3 6-dimetil 1 ((R) 1 morfolin-4-ilmetil-propil)-1H pirrolo[3 2 b]piridina

5 (6-Isopropil-2 metoxi piridin 3 il) 1 ((R) 1 metoximetil propil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{3-[3 6 Dimetil 1 ((R) 1 morfolin-4 ilmetil-propil) 1H-pirrolo[3 2 b]piridin 5 il]-6-isopropil piridin 2 il}-metil-amina

5 (2 Etil-6 isopropil piridin-3 il)-3 6-dimetil 1 ((R) 1 morfolin-4 ilmetil propil) 1H pirrolo[3 2 b]piridina

5-(2 Etil-6 isopropil pirıdın 3-il) 1 ((R) 1 metoxımetil propil)-3 6-dımetil 1H pırrolo[3 2 b]pırıdına

{6-Isopropil 3 [1-((R) 1 metoxımetil propil) 3 6-dimetil 1H pırrolo[3 2 b]pırıdın 5 il] pırıdın 2 il}-metil amına

5-(6 Isopropil pırıdın 3 il) 1 ((R) 1 metoxımetil-propil)-3 6-dımetil 1H pırrolo[3 2 b]pırıdına

6 Etil-5 (6 isopropil 2 metoxı-pırıdın 3 il) 1 ((S) 2 metoxı 1 metil-etil) 3-metil 1H pırrolo[3 2 b]pırıdına

(S) 2 [6 Etil 5 (6 isopropil 2 metoxı pırıdın 3 il) 3 metil pırrolo[3 2 b]pırıdın 1 il]-propan 1-ol

6 Etil 5-(6 isopropil pırıdın 3 il)-1 ((S) 2 metoxı 1 metil-etil)-3-metil 1H pırrolo[3 2 b]pırıdına

6-Etil 5 (2-etil-6 isopropil pırıdın-3 il) 1 ((S) 2 metoxı 1 metil-etil) 3-metil 1H pırrolo[3 2 b]pırıdına

{3-[6 Etil 1 ((S) 2 metoxı 1 metil-etil 3-metil 1H pırrolo[3 2 b]pırıdın 5-il]-6 isopropil pırıdın 2 il}-metil amına

(R)-1 [5 (6-Isopropil 2 metoxı pırıdın 3 il)-3 6-dimetil pırrolo[3 2 b]pırıdın 1 il] butan 1-ol

1 [5-(6 Isopropil 2 metoxı pırıdın-3-il)-3 6-dımetil pırrolo[3 2-b]pırıdın 1 il] 2 metil-propan 2-ol

5 (6-Isopropil-2 metoxı pırıdın 3-il) 1 ((R) 2-metoxı butil) 3 6-dimetil 1H pırrolo[3 2 b]pırıdına

(R) 2 [6-Etil 5 (6 isopropil 2 metoxı pırıdın-3 il) 3 metil pırrolo[3 2 b]pırıdın 1 il] propan 1-ol

(R) 2 [5 (2 Etoxı-6-etil 5-metanosulfonil-pırıdın 3 il)-6-etil-3 metil pırrolo[3 2 b]pırıdın 1 il] propan 1 ol

5-(2 Etoxı-6-etıl-5-metanosulfonıl-pırıdın-3-ıl)-6-etıl 1-((R) 2-metoxı 1-metıl-etıl) 3 metıl 1H-pırrolo[3 2 b]pırıdına

(R)-2 [6 Etıl 5 (6-ısopropıl 2 metoxı pırıdın 3-ıl) 3 metıl pırrolo[3 2 b]pırıdın 1 ıl] butan 1 ol

(R) 2 [5 (2 Etoxı-6-etıl 5 metanosulfonıl pırıdın 3-ıl)-6-etıl 3 metıl pırrolo[3 2 b]pırıdın 1 ıl] butan 1-ol

5-(2 Etoxı-6-etıl 5 metanosulfonıl pırıdın 3 ıl) 6-etıl 1 ((R) 1 metoxımetıl-propıl) 3-metıl 1H pırrolo[3 2-b]pırıdına

6-Etıl 5 (6-ısopropıl-2-metoxı pırıdın 3-ıl)-1 ((R) 1 metoxımetıl-propıl)-3-metıl 1H pırrolo[3 2 b]pırıdına

6 Etıl 5 (6-ısopropıl 2 metoxı pırıdın 3-ıl) 1 ((R) 2 metoxı 1 metıl-etıl) 3 metıl-1H pırrolo[3 2-b]pırıdına

5-(2-Azetıdın 1 ıl-6 ısopropıl pırıdın 3 ıl) 1 ((R) 1 metoxımetıl-propıl) 3 6-dımetıl 1H pırrolo[3 2-b]pırıdına

5 (2-Azetıdın 1 ıl-6-ısopropıl pırıdın 3 ıl)-6-etıl 1 ((R) 1 metoxımetıl-propıl) 3-metıl 1H pırrolo[3 2-b]pırıdına

{3 [6-Etıl 1 ((R) 1 metoxımetıl propıl) 3 metıl 1H pırrolo[3 2 b]pırıdın 5-ıl]-6 ısopropıl pırıdın 2 ıl}-metıl-amına

6 Etıl 5-(2-etıl-6 ısopropıl pırıdın 3 ıl)-1 ((R) 1 metoxımetıl propıl) 3 metıl 1H pırrolo[3 2 b]pırıdına

6-Etıl-5 (2-etıl-6 ısopropıl pırıdın 3 ıl) 1 ((R)-2 metoxı 1 metıl etıl) 3-metıl-1H pırrolo[3 2 b]pırıdına

{3-[6-Etıl-1 ((R) 2 metoxı 1 metıl-etıl) 3 metıl 1H pırrolo[3 2 b]pırıdın 5 ıl]-6 ısopropıl pırıdın 2 ıl}-metıl amına

6 Etıl 5-(4 ısopropıl 2 metoxı fenıl) 1 ((R) 2 metoxı-1-metıl-etıl) 3 metıl 1H pırrolo[3 2-b]pırıdına

6-Etil-1 ((R) 2 fluoro-1-metil-etil)-5-(4-isopropil-2-metoxi-fenil)-3-metil-1H pirrolo[3 2 b]piridina

6-Etil-1 ((R) 2 fluoró-1 metil-etil)-5-(6 isopropil-2 metoxi piridin 3 il) 3 metil-1H pirrolo[3 2 b]piridina

{5 Cloro-3 [7-cloro-6-etil 1 ((R) 2 metoxi 1 metil-etil) 3 metil-1H pirrolo[3 2 b]piridin-5-il]-6-isopropil-piridin-2-il}-metil-amina

{5-Cloro-3-[6-etil 1 ((R) 2-metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 il}-metil-amina

{5-Bromo-3-[6-etil 1 ((R) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil-piridin 2 il}-metil-amina

{5-Ciclopropil 3-[6-etil 1 ((R) 2 metoxi 1-metil-etil) 3 metil 1H pirrolo[3 2 b]piridin 5 il]-6 isopropil piridin 2 il}-metil-amina

{5-Etil 3 [6-etil-1-((R) 2 metoxi 1 metil-etil)-3 metil 1H pirrolo[3 2 b]piridin-5 il] 6-isopropil piridin 2 il}-metil-amina

(S) 2 [6 Bromo-5-(6-isopropil 2 metoxi piridin 3 il) 3 metil pirrolo[3 2 b]piridin 1 il] butan 1-ol

6-Bromo-5 (6 isopropil-2 metoxi-piridin 3 il) 1 ((S) 1-metoximetil propil) 3 metil 1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin-3 il) 1 ((S) 1 metoximetil-propil) 3 metil 1H pirrolo[3 2 b]piridina

5 Etil-6-[1 (1-etil propil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il] 3 isopropil 3H imidazo[4 5 b]piridina

Éster de bencilo de ácido (3S 4R) 3 (2 Fluoro-etoxi)-4 [5 (2 metoxi-4 trifluorometoxi-fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il] pirrolidino-1 carboxílico

Éster de metilo de ácido (3S 4R) 3-(2 Fluoro-etoxi)-4-[5 (2-metoxi-4 trifluorometoxi-fenil)-3 6-dimetil pirrolo[3 2 b]piridin 1 il]-pirrolidino-1 carboxílico

Éster de bencilo de ácido (3S 4R)-3-(2 Fluoro-etoxi)-4 [5 (6-isopropil 2 metoxi piridin 3 il) 3 6-dimetil-pirrolo[3 2 b]piridin 1 il] pirrolidino-1-carboxílico

Éster de metilo de ácido (3S 4R) 3-(2 Fluoro-etoxi)-4 [5-(6-isopropil 2 metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il]-pirrolidino-1 carboxílico

1 [(3R 4S)-4 (2 Fluoro-etoxi) 1 metanosulfonil pirrolidin-3-il] 5 (6 isopropil 2 metoxi piridin-3-il) 3 6-dimetil-pirrolo[3 2 b]piridina

1 [(3R 4S)-4-(2 Fluoro-etoxi) 1 metil pirrolidin-3 il] 5 (6 isopropil 2 metoxi piridin 3 il) 3 6-dimetil-1H pirrolo[3 2-b]piridina

Éster de 2 morfolin-4-il-etilo de ácido (3S 4R) 3 (2 Fluoro-etoxi)-4[5-(6 isopropil 2-metoxi-piridin 3 il) 3 6-dimetil-pirrolo[3 2 b]piridin 1 il] pirrolidino 1-carboxílico

3-Cloro-1 isopropil 5 (6 isopropil 2 metoxi piridin 3 il)-6 metil-1H pirrolo[3 2 b]piridina

3-Etil-5 (6 isopropil 2 metoxi-piridin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6-metil 1H pirrolo[3 2 b]piridina

3 Cloro-1 ((S) 2 metoxi 1 metil-etil)-5-(2 metoxi-4 trifluorometoxi fenil)-6 metil 1H pirrolo[3 2 b]piridina

3-Bromo-1 ((S) 2 metoxi 1 metil-etil) 5 (2-metoxi-4-trifluorometoxi fenil)-6 metil 1H pirrolo[3 2 b]piridina

1 ((S) 2 Metoxi 1 metil-etil) 5 (2 metoxi-4-trifluorometoxi fenil)-6 metil 1H pirrolo[3 2 b]piridina

3 Fluoro-1 ((S) 2-metoxi 1-metil-etil) 5-(2 metoxi-4 trifluorometoxi fenil)-6-metil-1H pirrolo[3 2-b]piridina

5-(6-Isopropil 2 metoxi piridin 3 il)-1 ((S)-2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2-b]piridina

3-Cloro 5-(6-isopropil 2 metoxi piridin 3-il) 1 ((S) 2 metoxi 1-metil-etil)-6-metil 1H-pirrolo[3 2 b]piridina

(R) 2 [5 (6-Isopropil 2 metoxi piridin 3-il)-6 metil pirrolo[3 2 b]piridin 1 il] butan 1 ol

3 Bromo-5-(6 isopropil-2 metoxi piridin-3 il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]piridina

(R) 2 [3 Cloro-5 (6 isopropil-2 metoxi piridin 3 il)-6-metil pirrolo[3 2-b]piridin l il] butan 1-ol

5-(6 Isopropil 2 metoxi piridin 3 il) 1 ((R) 1 metoximetil-propil)-6 metil 1H pirrolo[3 2 b]piridina

3 Cloro-5 (6-isopropil 2 metoxi piridin 3-il) 1 ((R) 1 metoximetil propil)-6-metil 1H pirrolo[3 2 b]piridina

1-[1 ((S) 2 Metoxi 1 metil-etil) 5 (2 metoxi-4 trifluorometoxi-fenil)-6 metil 1H pirrolo[3 2 b]piridin 7 il]-pirrolidino-2 5-diona

1 [5 (6-Isopropil 2 metoxi-piridin 3 il) 1 ((R) 1 metoximetil propil)-6 metil 1H pirrolo[3 2-b]piridin 7 il]-pirrolidino 2 5-diona

{3-[3-Cloro-1 ((S)-2 metoxi 1-metil-etil)-6 methyl 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil-piridin 2 il}-metil amina

{3-[3-Cloro-1 ((R) 1 metoximetil propil)-6 metil 1H pirrolo[3 2 b]piridin 5-il]-6 isopropil piridin 2 il}-metil-amina

3 Cloro-5 (2-etil-6 isopropil piridin 3 il) 1 ((S) 2-metoxi 1 metil-etil)-6-metil 1H pirrolo[3 2-b]piridina

3-Cloro-5 (6-isopropil piridin 3-il) 1-((S) 2-metoxi 1 metil-etil)-6-metil 1H pirrolo[3 2-b]piridina

6-Etil 7 [1 ((R) 1 hidroximetil propil) 3 6-dimetil-1H pirrolo[3 2 b]piridin 5-il]-4 isopropil 2 metil-4H pirido[2 3-b]pirazin 3-ona

6-Etil 2 4-diisopropil 7 [1 ((R) 1 metoximetil-propil)-3 6-dimetil 1H pirrolo[3 2 b]piridin 5-il]-4H pirido[2 3-b]pirazin 3-ona

2 6-Dietil-4 isopropil 7 [1 ((R) 1 metoximetil propil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-4H pirido[2 3-b]pirazin 3-ona

5 (6-Isopropil-2 metoxi piridin 3-il) 1 ((S) 2 metoxi 1 metil-etil)-6 metil 1H pirrolo[3 2 b]piridino-3-carbonitrilo

5 (6-Isopropil 2 metilamino-piridin 3 il) 1 ((S) 2 metoxi 1 metil-etil)-6-metil 1H pirrolo[3 2 b]piridino-3-carbonitrilo

6-Etil 7-[6-etil 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5 il]-4-isopropil-2 metil-4H pirido[2 3 b]pirazin 3 ona

5-(2 Etil-6-metoxi piridin 3 il) 1 isopropil 3 6-dimetil 1H pirrolo[3 2 b]piridina

5 (2 Etil-6 metoxi piridin 3 il) 1 ((S) 2 metoxi 1-metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(2 Etil-6-isopropoxi-piridin 3 il)-1 ((S) 2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2-b]piridina

{6 Etil-5 [1 ((S) 2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-dimetil-amina

5-(2 6 Dietil piridin 3-il) 1 ((S) 2 metoxi 1-metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5 (2 6 Dietil piridin 3 il) 1 isopropil 3 6-dimetil 1H pyr rolo[3 2 b]piridina

5-(2 Etil-6 isopropoxi piridin-3 il) 1 isopropil-3 6-dimetil 1H-pirrolo[3 2 b]piridina

[6 Etil-5-(1 isopropil 3 6-dimetil-1H pirrolo[3 2 b]piridin-5-il)-piridin 2 il]-dimetil amina

5 (6 Ciclopropilmetoxi-2-etil piridin 3-il) 1 ((S) 2 metoxi 1 metil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridina

2 [5 (6-Isopropil-2-metoxi piridin 3-il) 3 6-dimetil pirrolo[3 2-b]piridin 1 il] 2 metil-propan 1-ol

5-(6 Ciclopropil 2-etil piridin-3-il) 1 ((S) 2 metoxi 1-metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(6 Etoxi 2-etil piridin 3-il) 1 ((S) 2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin 3 il) 1 (2 metoxi 1 1-dimetil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

(R) 2-[5-(2 Etil-6-metoxi piridin 3 il) 3 6-dimetil pirrolo[3 2 b]piridin 1 il] butan 1 ol

6 Etil 2 metoxi-5-[1 ((S) 2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5-il] N metil-nicotinamida

5 (2 Etil-6 metoxi piridin 3 il) 1 ((R) 1 metoximetil propil)-3 6-dimetil-1H pirrolo[3 2 b]piridina

1-{6 Etil 2 metoxi-5 [1 ((S) 2-metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin-5-il] piridin 3-il}-etanona

5-(2 Etil-6 isopropil piridin 3-il) 1 (2 metoxi 1 1-dimetil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{6-Isopropil 3 [1 (2 metoxi 1 1-dimetil-etil)-3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il]-piridin 2 il}-metil amina

5-(6 Etoxi-2-etil piridin 3-il) 1 ((R) 1 metoximetil propil) 3 6-dimetil-1H pirrolo[3 2 b]piridina

5-(6-Ciclopropilmetoxi 2-etil-piridin-3 il)-1 ((R) 1 metoximetil propil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(2 Etil-6-isopropoxi-piridin 3 il) 1 ((R) 1 metoximetil propil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

6-Etil 5-(2-etil-6 metoxi piridin 3 il) 1 ((R) 2 fluoro-1 metoximetil-etil)-3-metil 1H-pirrolo[3 2 b]piridina

5 [2 Etil-6-(2 metoxi-etoxi) piridin 3-il] 1 ((S) 2 metoxi 1-metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metoxi piridin-3 il) 1 ((S) 2 metoxi 1 metil-etil)-3 6 7 trimetil-1H pirrolo[3 2 b]piridina

{6 Isopropil 3 [1 ((S) 2 metoxi 1 metil-etil) 3 6 7 trimetil 1H-pirrolo[3 2 b]piridin 5 il]-piridin 2 il}-metil amina

5-(2 Etil-6 isopropil piridin 3 il)-1 ((S) 2 metoxi 1 metil-etil) 3 6 7 trimetil 1H pirrolo[3 2 b]piridina

{6-Isopropil 3 [1 ((S) 2 metoxi 1 metil-etil) 3 6 7 trimetil 1H pirrolo[3 2 b]piridin 5-il] piridin 2 il}-dimetil amina

5-(2-azetidin 1 il-6 isopropil piridin 3-il) 1 ((S) 2 metoxi 1 metil-etil 3 6 7 trimetil- 1H pirrolo[3 2 b]piridina

[3-(3 6 Dimetil-1-propil 1H pirrolo[3 2-b]piridin 5 il)-6-isopropil piridin 2 il]-(2 metoxi-etil) amina

6 Isopropil 3 (1 isopropil-3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il)-piridin 2 il] (2 metoxi-etil)-amina

5-(6 Isopropil 2 metoxi piridin-3-il) 1 ((S) 2-metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridina

{6-Isopropil 3 [1 ((S) 2 metoxi 1 metil-etil)-3 6-dimetil-1H pirrolo[3 2 b]piridin 5 il]-piridin 2 il}-dimetil amina

[6 Isopropil 3 (1 isopropil 3 6-dimetil-1H pirrolo[3 2 b]piridin 5 il) piridin 2 il] dimetil-amina

[3-(3 6 Dimetil 1 propil 1H pirrolo[3 2 b]piridin 5-il)-6 isopropil piridin 2 il] dimetil-amina

5 (2-Azetıdın 1 ıl-6-ısopropıl pındın 3-ıl) 3 6-dımetıl 1 propıl 1H pırrolo[3 2 b]pındına

5-(2-Azetıdın 1 ıl-6 ısopropıl pındın 3-ıl) 1 ısopropıl 3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

5-(2-Azetıdın 1 ıl-6 ısopropıl-pındın-3 ıl) 1 ((S) 2 metoxı 1 metıl-etıl)-3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

5 [2 (3 3 Dıfluoro-azetıdın 1 ıl)-6 ısopropıl pındın 3-ıl]-1 ((S) 2 metoxı 1 metıl etıl) 3 6-dımetıl 1H pırrolo[3 2-b]pındına

5 (2 Etoxı-6-ısopropıl pındın-3 ıl) 1 ((S) 2-metoxı 1 metıl-etıl) 3 6-dımetıl 1H pırrolo[3 2 b]pındına

5-(2 Isopropoxı-6-ısopropıl pındın 3 ıl) 1 ((S) 2 metoxı 1 metıl-etıl]-3 6-dımetıl 1H pırrolo[3 2 b]pındına

5-(6 Isopropıl 2-metıl-pındın 3 ıl) 1 ((S) 2 metoxı 1 metıl-etıl)-3 6-dımetıl 1H pırrolo[3 2 b]pırıdına

[3-(3 6-Dımetıl 1 propıl-1H pırrolo[3 2 b]pındın 5-ıl)-6 ısopropıl-pındın 2 ıl] ısopropıl amına

Isopropıl [6 ısopropıl 3 (1 ısopropıl 3 6-dımetıl 1H pırrolo[3 2-b]pındın 5 ıl) pındın 2 ıl]-amına

{6 Isopropıl 3-[1 (2-metoxı 1 metıl-etıl) 3 6-dımetıl 1H pırrolo[3 2 b]pırıdın 5-ıl] pırıdın 2 ıl}-(2 metoxı-etıl)-amına

Isopropıl-{6-ısopropıl 3-[1-((S) 2 metoxı 1 metıl-etıl) 3 6-dımetıl 1H pırrolo[3 2 b]pındın 5-ıl]-pındın 2 ıl}-amına

Etıl-{6-ısopropıl 3-[1 ((S) 2 metoxı-1 metıl-etıl) 3 6-dımetıl 1H pırrolo[3 2 b]pındın 5 ıl] pındın 2 ıl}-amına

1 Isopropıl-5-[6 Isopropıl 2 (4-metıl pıperazın 1 ıl) pındın 3 ıl] 3 6-dımetıl 1H pırrolo[3 2 b]pındına

[5-Cloro-6 isopropil 3 (1 isopropil 3 6-dimetil 1H-pirrolo[3 2 b]piridin 5-il) piridin 2 il]-etil amina

1 Isopropil-5-(6 isopropil 2-metil-piridin 3-il) 3 6-dimetil-1H pirrolo[3 2 b]piridina

5-(6 Isopropil 2 metil piridin 3 il) 3 6-dimetil 1 propil 1H pirrolo[3 2 b]piridina

1 Isopropil-5-(6 isopropil piridin 3-il) 3 6-dimetil 1H pirrolo[3 2 b]piridina

5 (6 Isopropil 2 metoxi piridin 3-il)-6-metoxi-1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridina

Ciclopropil-{6 isopropil-3-[1 ((S) 2 metoxi 1 metil-etil) 3 6-dimetil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-amina

5-(6-Isopropil-piridin-3-il)-6-metoxi 1 ((S) 2 metoxi-1 metil-etil) 3 metil 1H pirrolo[3 2 b]piridina

5-(2 Etil-6-isopropil piridin 3 il)-6-metil 1 ((S) 2-metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridina

Etil-{6 isopropil 3 [6 metoxi 1 ((S) 2-metoxi-1 metil-etil) 3 metil 1H-pirrolo[3 2 b]piridin 5 il]-piridin 2 il}-amina

{6-Isopropil 3 [6-metoxi 1 ((S) 2 metoxi 1 metil-etil)-3-metil 1H pirrolo[3 2 b]piridin 5-il] piridin 2 il}-dimetil amina

{6 Isopropil-3-[6-metoxi 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridin 5 il] piridin 2 il}-metil-amina

6-Cloro-5 (6 isopropil 2 metoxi-piridin 3 il) 1 ((S) 2-metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridina

6-Cloro-5 (2-etil-6 isopropil piridin 3 il) 1 ((S) 2 metoxi 1 metil-etil) 3 metil-1H pirrolo[3 2 b]piridina

6-Cloro-5-(6 isopropil-piridin 3 il) 1 ((S) 2 metoxi 1 metil-etil) 3-metil 1H pirrolo[3 2 b]piridina

{3 [6-Cloro-1 ((S) 2 metoxi 1 metil-etil) 3-metil-1H pirrolo[3 2 b]piridin 5 il]-6-isopropil piridin 2 il}-dimetil-amina

{3 [6-Cloro-1 ((S) 2 metoxı 1 metıl-etıl) 3-metıl-1H pırrolo[3 2 b]pırıdın 5 ıl]-6-ısopropıl pırıdın 2 ıl}-metıl-amına

{3 [6-Cloro 1-((S) 2 metoxı 1 metıl-etıl) 3 metıl 1H pırrolo[3 2 b]pırıdın 5 ıl]-6-ısopropıl pırıdın 2 ıl}-etıl-amına

{3 [6-Cloro-1 ((R) 1 fluorometıl-2 metoxı-etıl) 3-metıl 1H pırrolo[3 2 b]pırıdın-5-ıl]-6 ısopropıl-pırıdın 2 ıl}-metıl-amına

6-Cloro-5 (2-etıl-6 ısopropıl pırıdın 3 ıl) 1 ((R) 1 fluorometıl 2 metoxı-etıl) 3 metıl 1H pırrolo[3 2 b]pırıdına

6 Cloro-1 ((R) 1 fluoro-metıl 2-metoxı-etıl)-5-(6-ısopropıl 2 metıl pırıdın 3-ıl) 3 metıl 1H-pırrolo[3 2 b]pırıdına

{5-Cloro-3 [1 ((R) 1 fluorometıl 2 metoxı-etıl) 3 6-dımetıl-1H pırrolo[3 2 b]pırıdın 5-ıl]-6 ısopropıl pırıdın 2 ıl}-metıl-amına

1 (R) 1 Fluorometıl 2 metoxı-etıl) 5 (6 ısopropıl 2 metıl-pırıdın-3-ıl) 3 6-dımetıl 1H-pırrolo[3 2 b]pırıdına

Etıl-{3 [1 ((R) 1 fluorometıl 2 metoxı-etıl) 3 6-dımetıl 1H-pırrolo[3 2 b]pırıdın 5 ıl] 6 ısopropıl pırıdın 2 ıl}-amına

2 Bromo-7 (1-etıl propıl)-3-(2 metoxı-4 trıfluorometoxı-fenıl) 5 metıl 5H pırrolo[2 3 b]pırazına

7 (1 Etıl propil) 3 (2 metoxı-4 trıfluorometoxı-fenıl) 5 metıl 5H pırrolo[2 3-b]pırazına

2 Etıl 7 (1-etıl propıl) 3 (2 metoxı-4 trıfluorometoxı fenıl) 5 metıl-5H pırrolo[2 3 b]pırazına

7 (1 Etıl propıl) 3-(2 metoxı-4 trıfluorometoxı-fenıl) 2 5-dımetıl 5H pırrolo[2 3 b]pırazına

2 Etıl 7 (1-etıl propıl)-3-(6-ısopropıl 2-metoxı-pırıdın-3-ıl) 5 metıl-5H pırrolo[2 3-b]pırazına

2 Etil 3 (2-etil-6 isopropil-piridin 3-il) 7 (1-etil propil) 5 metil 5H pirrolo[2 3-b]pirazina

{3-[2 Etil 7 (1-etil propil)-5-metil 5H pirrolo[2 3 b]pirazin-3-il]-6 isopropil-piridin 2 il}-metil-amina

Dietil-[4-etil-5-[2-etil 7 (1-etil propil) 5-metil-5H pirrolo[2 3-b]pirazin 3-il]-piridin 2 il}-amina

2 Etil 7 (1-etil-propil) 3 (3 isopropil-5 metoxi 2 3-dihidro-furo[3 2 b]piridin-6 il) 5 metil 5H pirrolo[2 3 b]pirazina

2 [3-(2 Metoxi-4 trifluorometoxi fenil) 2 5-dimetil-5H pirrolo[2 3-b]pirazin 7 il]-propan 1-ol

7 (2 Metoxi 1 metil-etil) 3-(2 metoxi-4-trifluorometoxi fenil) 2 5-dimetil 5H pirrolo[2 3 b]pirazina

Éster de metilo de ácido 2 [3 (2 Metoxi-4 trifluorometoxi fenil) 2 5-dimetil-5H pirrolo[2 3 b]pirazin 7 il]-propionico

2-[3-(6 Isopropil 2 metoxi piridin-3-il) 2 5-dimetil 5H pirrolo[2 3-b]pirazin 7 il] propan 1-ol

Éster de 2 [3-(6-isopropil 2-metoxi piridin-3-il) 2 5-dimetil-5H pirrolo[2 3 b]pirazin 7 il] propilo de ácido Metanosulfónico

3-(6-Isopropil 2 metoxi-piridin 3 il) 7 (2 metoxi 1-metil-etil)-2 5-dimetil 5H pirrolo[2 3 b]pirazina

3-(6 Isopropil 2 metoxi piridin-3 il) 2 5-dimetil 7 (1 metil 2 morfolin-4-il-etil) 5H pirrolo[2 3-b]pirazina

7-sec-Butil 3 (6 isopropil 2 metoxi-piridin 3 il) 2 5-dimetil 5H pirrolo[2 3 b]pirazina

7 Isopropil 3-(6-isopropil 2 metoxi pindin 3 il) 2 5-dimetil 5H pirrolo[2 3 b]pirazina

2 [3-(6-Isopropil 2 metoxi piridin 3 il)-2 5-dimetil 5H pirrolo[2 3 b]pirazin 7 il] butan 1-ol

3 (6 Isopropil 2 metoxi piridin-3-il) 7 (1 metoximetil propil) 2 5-dimetil 5H pirrolo[2 3-b]pirazina

Éster de 2 [3-(6 isopropil 2 metoxi piridin 3 il) 2 5-dimetil-5H pirrolo[2 3-b]pirazin 7 il] butilo de ácido Metanosulfónico

2 Etil 7 isopropil 3-(6-isopropil 2 metoxi-piridin 3-il) 5 metil 5H pirrolo[2 3 b]pirazina

3-(2 Etil-6-isopropil-piridin 3 il) 7 (2 metoxi 1 metil-etil) 2 5-dimetil 5H pirrolo[2 3 b]pirazina

2 Etil 3 (2-etil-6 isopropil piridin 3 il) 7 isopropil 5 metil 5H pirrolo[2 3 b]pirazina

[3-(2 Etil-7 isopropil-5-metil-5H pirrolo[2 3-b]pirazin 3 il)-6 isopropil piridin 2 il] metil amina

{6 Isopropil 3 [7 (2 metoxi 1 metil-etil) 2 5-dimetil 5H pirrolo[2 3 b]pirazin 3-il] piridin 2 il}-metil amina

{4-Etil 5-[2-etil 7-(1-etil-propil) 5-metil 5H pirrolo[2 3-b]pirazin 3-il] piridin 2 il}-dimetil-amina

Etil-{4-etil 5 [2-etil 7 (1-etil propil) 5-metil 5H pirrolo[2 3-b]pirazin 3 il]-piridin 2 il}-metil-amina

2 2 Dietil 7 7 bis (1-etil propil) 5 5 -dimetil 5H 5 H [3 3']bi[pirrolo[2 3-b]pirazinil]

5-Etil-6 [2-etil 7 (1-etil propil) 5 metil-5H pirrolo[2 3-b]pirazin 3 il] 3 isopropil 3H imidazo[4 5-b]piridina

2 Etil 7 (2 metoxi-etil) 3-(2-metoxi-4-trifluorometoxi fenil) 5 metil-5H pirrolo[2 3-b]pirazina

3-[2 Etil 3-(2 metoxi-4-trifluorometoxi-fenil)-5 metil-5H pirrolo[2 3-b]pirazin 7 il]-propiontrilo

5-Bromo-3 (1-etil propil)-6 (2 metoxi-4-trifluorometoxi fenil) 1 metil 1H pirrolo[2 3-b]piridina

3 (1 Etil propil)-6 (2 metoxi-4 trifluorometoxi fenil) 1 5-dimetil 1H pirrolo[2 3-b]piridina

5-Cloro 3-(1-etil propil)-6-(2 metoxi-4 trifluorometoxi fenil) 1 metil 1H pirrolo[2 3-b]piridina

3 (1 Etil-propil)-6 (2 metoxi-4 trifluorometoxi fenil)-1 5-dimetil 1H pirrolo[2 3-b]piridina

3-sec-Butil-6-(6-isopropil-2-metoxi piridin 3 il) 1 5-dimetil-1H pirrolo[2 3-b]piridina

3-sec-Butil-6 (2-etil-6 isopropil piridin 3 il)-1 5-dimetil-1H-pirrolo[2 3-b]piridina

[3 (3-sec-Butil 1 5-dimetil 1H pirrolo[2 3-b]piridin-6 il)-6-isopropil piridin 2 il]-metil-amina

2 [6 (6-Isopropil 2 metoxi-piridin 3 il)-1 5-dimetil-1H pirrolo[2 3-b]piridin 3 il] butan 1-ol

6 (6-Isopropil 2 metoxi piridin 3-il) 3 (1-metoxi metil propil) 1 5-dimetil 1H pirrolo[2 3 b]piridina

5-Bromo-3 isopropil-6 (6 isopropil 2 metoxi piridin 3 il)-1 metil 1H pirrolo[2 3 b]piridina

3 Isopropil-6 (6 isopropil 2 metoxi piridin 3-il) 1 5-dimetil 1H pirrolo[2 3 b]piridina

3 (1 Etoximetil propil)-6-(6-isopropil 2 metoxi piridin 3 il) 1 5-dimetil 1H pirrolo[2 3 b]piridina y

5-Etil 3 isopropil- 6 (6 isopropil 2-metoxi piridin 3 il) 1 metil 1H pirrolo[2 3 b]piridina

42 Un compuesto o sal de acuerdo con una cualquiera de las Reivindicaciones 1-41 en donde en un ensayo de unión de receptor CRF estándar in vitro el compuesto exhibe un valor IC_{50} para receptores CRF de menos de o igual a 1 micromolar

43 Un compuesto o sal de acuerdo con una cualquiera de las Reivindicaciones 1-41 en donde en un ensayo de unión de receptor CRF estándar in vitro el compuesto exhibe un valor IC_{50} para receptores CRF de menos de o igual a 100 nanomolar

44 Un compuesto o sal de acuerdo con una cualquiera de las Reivindicaciones 1-41 en donde en un ensayo de unión de receptor CRF estándar in vitro el compuesto exhibe un valor IC_{50} para receptores CRF de menos de o igual a 10 nanomolar

45 Un método para tratar un desorden de ansiedad un desorden relacionado con el estrés o desorden de alimentación comprende administrar a un paciente en necesidad de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto o sal de acuerdo con una de las Reivindicaciones 1-41

46 Un método para tratar una depresión o desórdenes bipolares comprende administrar a un paciente en necesidad de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto o sal de acuerdo con una de las Reivindicaciones 1-41

47 Un método para tratar anorexia nerviosa bulimia nerviosa u obesidad comprende administrar a un paciente en necesidad de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto o sal de acuerdo con una de las Reivindicaciones 1-41

48 Un compuesto o sal de acuerdo con cualquiera de las Reivindicaciones 1 41 en donde en un ensayo funcional de canal Na in vitro estándar el compuesto no muestra ninguna actividad moduladora de canal Na detectable estadísticamente significativa en el nivel $p < 0.05$ de significancia en un ensayo paramétrico estándar de importancia estadística

49 Un método para demostrar la presencia de receptores CRF en muestras de células o tejidos dicho método comprende

preparar una pluralidad de muestras de tejidos de células o tejidos emparejados

preparar al menos una muestra de control al poner en contacto (bajo condiciones que permiten la unión de CRF a receptores CRF dentro de muestras de célula de tejido) al menos una de las muestras de célula o tejido emparejadas (que no se han puesto previamente en contacto con cualquier compuesto o sal de cualquiera de las Reivindicaciones 1-41) con una solución de control que comprende una preparación etiquetada detectablemente de un compuesto seleccionado o una sal de cualquiera de las Reivindicaciones 1-41 en una primera concentración molar medida dicha solución de control comprende adicionalmente una preparación no etiquetada del compuesto seleccionado o sal en una segunda

concentración molar medida cuya segunda concentración medida es mayor que dicha primera concentración medida

preparar al menos una muestra experimental al poner en contacto (bajo condiciones que permiten la unión del CRF a receptores CRF dentro de muestras de célula y tejidos) al menos una de las muestras de célula o tejido emparejadas (que no se han puesto previamente en contacto con cualquiera de los compuestos o sales de cualquiera de las reivindicaciones 1-41) con una solución experimental que comprende la preparación etiquetada detectablemente del compuesto seleccionado o sales en una primera concentración molar medida dicha solución experimental no comprende adicionalmente una preparación no etiquetada de cualquier compuesto o sal de cualquiera de las reivindicaciones 1-41 en una concentración mayor de o igual a dicha primera concentración medida

lavar al menos una muestra de control para remover el compuesto seleccionado no unido o sal para producir al menos una muestra de control lavada

lavar al menos una muestra experimental para remover el compuesto seleccionado no unido o sal para producir al menos una muestra experimental lavada

medir la cantidad de etiqueta detectable de cualquier compuesto seleccionado etiquetado detectablemente de unión restante o sal en al menos una muestra de control lavada

medir la cantidad de etiqueta detectable de cualquier compuesto seleccionado etiquetado detectablemente de unión restante o sal en al menos una muestra experimental lavada

comparar la cantidad de etiqueta detectable medida en cada una de al menos una muestra experimental lavada a la cantidad de etiqueta detectable medida en cada uno de al menos una muestra de control lavada

en donde una comparación que indica la detección de una cantidada mayor de etiqueta detectable en al menos una muestra experimental lavada que se detecta en cualquiera de al menos una muestra de control lavada que demuestra la presencia de receptores CRF en esa muestra experimental

50 Un método para inhibir la unión de CRF a un receptor CRF1 tal método comprende

poner en contacto una solución que comprende CRF y un compuesto o sal de cualquiera de las Reivindicaciones 1 a 41 con una célula que expresa el receptor CRF en donde el compuesto o sal está presente en la solución en una concentración suficiente para inhibir la unión CRF in vitro a células IMR32

51 El método de la Reivindicación 50 en donde la célula que expresa el receptor CRF es una célula neuronal que está puesta en contacto in vivo en un animal y en donde la solución es un fluido corporal de dicho animal

52 El método de la Reivindicación 51 en donde el animal es un paciente humano

53 Una composición farmacéutica comprende un portador farmacéuticamente aceptable y un compuesto o sal de cualquiera de las Reivindicaciones 1 41

531

54 Un paquete que comprende una composición farmacéutica de la Reivindicación 53 en un contenedor y comprende adicionalmente indicios que comprenden al menos una de

instrucciones para usar la composición para tratar un paciente que sufre de un desorden de ansiedad o

instrucciones para utilizar la composición para tratar un paciente que sufre de un desorden relacionado con el estrés o

instrucciones para utilizar la composición para tratar un paciente que sufre de un desorden alimenticio

55 Un paquete que comprende una composición farmacéutica de la Reivindicación 53 en un contenedor y comprende adicionalmente indicios que comprenden al menos una de instrucciones para utilizar la composición para tratar un paciente que sufre de depresión o instrucciones para utilizar la composición para tratar un paciente que sufre de un desorden bipolar

FOLIO 532 PARA PUBLICACIÓN.

2006-07-06

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Dependenc 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA 06 22 305
FECHA MARZO 21 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No PAGO	FECHA PGO	V PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050 00110-6	49935722	21/03/2006	40 671 320 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	463 000 00
			TOTAL $	463 000 00

SON CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No _____

Rdo 15271-891001 /

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SUPERINDUSTRIA Y COMERCIO
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Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

PCT

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (X) MODELO DE UTILIDAD ( )	( )	( )
Indicación de que se solicita la concesión de una patente.	( )	(X)
Datos de identificación del solicitante o de la persona q e se presenta la solicitud	( )	(X)
Descripción de la invención	( )	(X)
Dibujos de ser estos pertinentes	( )	(X)
C mprobante d Pago d la tasas establecidas	( )	(X)
COMPLETA (X) INCOMPLETA ( )	( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación d qu se olicita el registro de Dis ño I dustrial	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud	( )	( )
Representación gráfica y fotográfi a del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprob nte de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )
ESQUEMA DE TRAZADO ( )		
Indi ación de q se solicita el registro de Diseño Industrial.	( )	( )
Datos de identificación del solicitante d la persona que se presenta la solicitud	( )	( )
Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA ( )	( )	( )

Firm Respons ble _____

Fecha _____

Extracto folio 532

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá
2020

Do to (a)
FERRERO EMILIO
Apode ado(a) y/o Repre entant de
NEUROGEN CORPORATION
AVENTIS PHARMACEUTICALS INC

REFERENCIA	Radi ación N	06 31674
	Soli itud int rna ional	US2004/028899
	Fecha ini io fase na ional	05/04/2006
	T ámit	11
	Evento	378
	Actua ión	430
	Ofi io No	7729

Como resultado del examen de forma reali ado con fundament en l artículo 38 de la De i ión 486 de la Comi ión de la Comunidad Andina artículo 27 del T atado de Coopera ión en Materia de Patent (PCT) regla 51 bi del Reglamento y Ci cular Úni a de la Supe intendencia de Indust ia y Comer i l comunica que

1 La li itud no ontiene la copia del documento en que consta la ión del de ho a l patent del invento al oli itant o a u causant (Art 26 k) De i ión 486

2 El oli itante deb aclara i la oli itud corre ponde al capítulo I o II del PCT por que no fue indicado en el petito io Si fue a l ca o adjuntar el anexo del repo t de examen p limina

En cumplimiento de l di pue to po l artículo 39 de la Deci ión 486 le requi re para que dentro del término de do me e iguient a la fecha de notifi a ión del p ent ofi io compl te lo equi ito ant riorment enunciado En ca o de no dar cumplimiento al pre ent reque imiento la oli itud con ider á abandonada y perde á u p el ión

Notifíque l pre ent ofi io conforme a lo di pue to en el nume al 5 2 lit al) del apítulo quinto del título p imero de la Ci cula Unica N 10 de 2001

ALIX CARMENZA CESPEDES DE VERGEL
J f de la divi ión de Nueva Crea ione

El ant io reque imiento fue notificado por fijación en li ta de fecha_____
j amo 27 JUL 2006

30 60-12