SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Organizacion CSA Ltda

# Industria y Comercio

SUPERINTENDENCIA

NOV 27 PCT

**DELEGATURA DE PROPIEDAD INDUSTRIAL**

**DIVISIÓN DE NUEVAS CREACIONES**

07-129906

**SOLICITUD DE PATENTE DE INVENCIÓN**

**TITULO:** INHIBIDORES DE LA ACTIVIDAD AKT

**SOLICITANTE:** MERCK & CO., INC.

**DIRECCIÓN:** 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907. E.U.A.

**APODERADO:** CARLOS R. OLARTE

**BOGOTÁ** 06 de Diciembre de 2007

P2007/000187

# OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-129906- -00000-0000
Fecha: 2007-12-07 16:35:03 Dep: 2020 NUECREACIONI
Tipo: 11 PATENTEIYII Eve: 379 FASENACIONALII
Clase: 411 PRESENTACION Folios: 334

**PETITORIO - FORMULARIO**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL** 10 ene 2008 **P2007/000187**

**SOLICITUD DE:**

(1) [X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**

**Nombre:** MERCK & CO., INC.
**Dirección:** 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907
**Nacionalidad o Domicilio:** ESTADOS UNIDOS
**Lugar de Constitución:** ESTADOS UNIDOS
**Teléfono:** **Fax:**
**E-mail:**

**IDENTIFICACIÓN**
**C.C.** [ ] **NIT** [ ]
**C.E.** [ ] **Otro** [ ]
**Cual**
**Número**

**REPRESENTANTE O APODERADO**

**Nombre:** CARLOS R. OLARTE
**Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
**Teléfono:** 601-7700 **Fax:** 601-7799
**E-mail:** office@olarteraisbeck.com

**IDENTIFICACIÓN**
**C.C.** [X] **NIT** [ ]
**C.E.** [ ] **Otro** [ ]
**Cual**
**Número** 79782747Bta
**TP** 74.295

**INVENTOR (ES) (72)**

**Nombre:** VER PAGINA ADJUNTA
**Dirección:** VER PAGINA ADJUNTA
**Nacionalidad o Domicilio:** VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2006/022079 Fecha Junio 7, 2006

Publicación Internacional No. WO 2006/135627 Fecha Diciembre 21, 2006

(6) **Título (54)** INHIBIDORES DE LA ACTIVIDAD AKT

(7) **Clasificación Internacional (51)** A61K 31/397

(8) **Prioridad** **SI** [X] **NO** [ ]

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| US | Junio 10, 2005 | 60/689.726 |
| US | Noviembre 7, 2005 | 60/734.188 |
| | | |
| | | |

(9) **Comprobante de pago No.** 07-98.627 **Fecha** Diciembre 4, 2007

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-055.540
- [x] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional 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 12 x 12.
- [ ] 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.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

( ) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

**DONNA J. ARMSTRONG,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

**ESSA H. HU,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

**MICHAEL J. KELLY III,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

**MARK E. LAYTON,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

**YIWEI LI,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Canadiense

**JUN LIANG,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Canadiense

**KEVIN J. RODZINAK,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

**MICHAEL A. ROSSI,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

**PHILIP E. SANDERSON,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Británica

**JIABING WANG,**
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-129906- -00000-0000

Fecha: 2007-12-07 16:35:03 Dep: 2020 NUECREACIONI
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Act: 411 PRESENTACION Folios: 334

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 98,627
FECHA : DICIEMBRE 4 DE 2007

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| OLARTE RAISBEK | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 68286500 | 03/12/2007 | 6,123,000.00 |

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

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

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

**PODER ESPECIAL**

Yo el abajo firmante, J. Ian Raisbeck, identificado con cédula de ciudadanía No. 79.376.996 de Bogotá, representante legal de OLARTE RAISBECK & FRIERI LTDA., sociedad limitada constituida en la República de Colombia, y obrando bajo las facultades otorgadas por el Poder General adjunto por la sociedad MERCK & Co. Inc., constituida de acuerdo a las leyes de New Jersey, Estados Unidos de América domiciliada en 126 East Lincoln Avenue, Rahway, NJ 07065-0907, Estados Unidos de América, nombro por el presente a los Doctores CARLOS R. OLARTE y/o ANA MARIA FRIERI DEL CASTILLO y/o JUAN GUILLERMO MOURE PEREZ y/O NATALIA CASTRO VELEZ, para que representen a la sociedad MERCK & Co. Inc., en la Republica de Colombia, en materia de patentes, y ante las autoridades ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses. Por el presente instrumento se revoca todo poder anteriormente otorgado por mi representada para realizar las gestiones antes mencionadas.

Dado y firmado el 28 de Mayo de 2007

J. IAN RAISBECK

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA
NOTARIA EL ARTICULO PUESTO PRESENTADO AL
27
Con C.C.
Y MANIFESTO QUE LA FIRMA QUE APARECE EN EL
EL DECLARANTE:
HOY: 01 MAY 2015
HUELLA
MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

Juan Pacheco
79376996 3b1p13579905

REPUBLICA DE COLOMBIA
MARÍA EUGENIA ROJAS DE URUETA
NOTARIA
Bogotá D.C.

WK 4682369

ESCRITURA PUBLICA NUMERO - - - - - -
TRESCIENTOS DOCE (312).- - - - - - - - - - -
En la ciudad de Bogotá, Distrito Capital, República de Colombia, a los Veintidos - - - ( 22 ) días del mes de Marzo - - - - - de dos mil siete (2007), ante mi, MARIA EUGENIA ROJAS DE URUETA - - - - - - - - - - - - - - - - - - NOTARIA(O) VEINTISIETE (27) DEL CIRCULO DE BOGOTA, - - - se otorgó la escritura pública que se consigna en los siguientes términos: ----------

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CLASE(S) DE ACTO: PROTOCOLIZACION: ----------
**OLARTE RAISBECK & FRIERI LTDA**----------
NIT: 830122870-6.----------

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Compareció **CARLOS REINALDO OLARTE GARCIA** mayor de edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.782.747, obrando en nombre y representación **OLARTE RAISBECK & FRIERI LTDA**, con número de identificación tributaria (NIT) 830122870-6 entidad legalmente constituida mediante escritura pública número mil ciento diecinueve (1119) de la notaría treinta y nueve (39) de Bogotá del diez (10) de junio de dos mil tres (2003), como lo acredita con el certificado de constitución y gerencia expedido por la Cámara de Comercio de Bogotá que presenta para su protocolización y declaró ----------

**PRIMERO.**- Que presenta para su protocolización y custodia en los archivos de ésta notaría, bajo el número y lugar que a ésta escritura corresponda, en cinco (5) folios autenticados, un poder con su traducción la cual es del siguiente tenor:----------

PODER GENERAL ----------

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

El suscrito, MERCK & CO., INC, domiciliado en 126 EAST LINCOLN AVENUE, RAHWAY, NJ 07065-0907, USA.----------
nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con Oficinas en el World Trade Center Torre A, Calle 100 No. 8A-37, piso 10, Bogotá D.C. nuestro representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia y la República del Ecuador, la Republica del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de Policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales, elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento allanarse a la pretensión, recibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.- ----------

Firma: Donna L. Margiotto, Senior Manager, "Patent----------

*01*

*5647161 1*

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

1 DE FEBRERO DE 2007 HORA 09:15:34

02C25020105804PCT0708 HOJA : 001

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS.
LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL,

CERTIFICA :

NOMBRE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK
N.I.T. : 830122870-6 ADMINISTRACION: BOGOTA PERSONAS JURIDICAS, REGIMEN COMUN.
DOMICILIO : BOGOTA D.C.

CERTIFICA :

MATRICULA NO. 01284164

CERTIFICA :

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD COMERCIAL DENOMINADA: OR LEGAL LTDA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001328 DE NOTARIA 39 DE BOGOTA D.C. DEL 4 DE JULIO DE 2003 , INSCRITA EL 9 DE JULIO DE 2003 BAJO EL NUMERO 00887749 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : OR LEGAL LTDA POR EL DE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK

CERTIFICA :

REFORMAS:

| ESCRITURA | FECHA | NOTARIA | CIUDAD | INSCRIPCION | FECHA |
|---|---|---|---|---|---|
| 0001328 | 2003/07/04 | 00039 | BOGOTA D.C. | 00887749 | 2003/07/09 |

CERTIFICA :

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 10 DE JUNIO DE 2103 .

CERTIFICA :

OBJETO SOCIAL : LA SOCIEDAD TENDRA POR OBJETO PRINCIPAL LA PRESTACION DE SERVICIOS DE ASESORIA EN EL AREA SOCIAL, TECNICA, COMERCIAL Y JURIDICA, DE PERSONAS NATURALES O JURIDICAS, NACIONALES O EXTRANJERAS, PUBLICAS O PRIVADAS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA : A. PRESTAR ASESORIA Y EJERCER LA REPRESENTACION JUDICIAL DE PERSONAS NATURALES O JURIDICAS ANTE LAS DIFERENTES JURISDICCIONES Y PARTICIPAR EN SU NOMBRE Y REPRESENTACION EN TRIBUNALES DE ARBITRAMENTO, AMIGABLE COMPOSICION, CONCILIACION Y MEDIACION. B. CONFORMAR Y PARTICIPAR EN CENTROS DE ARBITRAJE Y CONCILIACION. C. CELEBRAR Y EJECUTAR TODAS LAS OPERACIONES DE CAMBIO Y COMERCIO EXTERIOR QUE REQUIERA EL BUEN FUNCIONAMIENTO DE LA COMPAÑIA ; D. ADQUIRIR, ENAJENAR, GRAVAR, DAR O TOMAR EN ARRENDAMIENTO TODA CLASE DE BIENES, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ;

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

E. INTERVENIR COMO DEUDORA O ACREEDORA EN TODA CLASE DE OPERACIONES DE CREDITO, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ; F. CELEBRAR CON ESTABLECIMIENTOS DE CREDITO NACIONALES O EXTRANJEROS Y CON COMPAÑIAS ASEGURADORAS TODAS LAS OPERACIONES QUE SE RELACIONEN CON LOS NEGOCIOS Y BIENES SOCIALES. G. ABRIR, OPERAR Y CERRAR CUALQUIER TIPO DE CUENTAS BANCARIAS ; H. GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, COBRAR, RECHAZAR, PROTESTAR, AVALAR GARANTIZAR Y NEGOCIAR EN GENERAL TODA CLASE DE INSTRUMENTOS NEGOCIABLES Y CUALQUIER OTRA CLASE DE TITULOS DE CREDITO ; I. ORGANIZAR, PROMOVER, FORMAR Y FINANCIAR SOCIEDADES O EMPRESAS NACIONALES O EXTRANJERAS QUE TIENDAN A FACILITAR, ENSANCHAR, O COMPLEMENTAR LOS NEGOCIOS SOCIALES DENTRO Y FUERA DEL PAIS Y SUSCRIBIR ACCIONES O CUOTAS EN ELLAS, Y EJERCER TODOS LOS DERECHOS Y OBLIGACIONES ECONOMICOS Y CORPORATIVOS QUE SURJAN DE DICHA PARTICIPACION. J. CREAR CONSORCIOS Y UNIONES TEMPORALES. K. SERVIR DE COMISIONISTA O INTERMEDIARIO COMERCIAL A TITULO DE CORRETAJE O A CUALQUIER OTRO TITULO ; I. SER CORRESPONSAL Y TENER CORRESPONSALES INTERNACIONALES ; M. EFECTUAR AVALUOS COMERCIALES DE TODA CLASE DE BIENES. N. ADQUIRIR Y CONSTRUIR TODA CLASE DE INSTALACIONES INDUSTRIALES O COMERCIALES COMO FABRICAS, TALLERES, ALMACENES DE DISTRIBUCION O VENTA ESTABLECIMIENTOS DE COMERCIO, ETC. O. DISTRIBUIR O VENDER TODO TIPO DE PRODUCTOS Y ABRIR Y ADMINISTRAR, DIRECTA O INDIRECTAMENTE, LOS ESTABLECIMIENTOS DE COMERCIO QUE SEAN NECESARIOS PARA ELLO. P. ENAJENAR, ARRENDAR, GRAVAR Y ADMINISTRAR EN GENERAL LOS BIENES QUE COMPONEN EL PATRIMONIO SOCIAL. Q. APORTAR SUS BIENES, EN TODO O EN PARTE, A OTRA U OTRAS SOCIEDADES A QUE LE CONVENGA VINCULARSE PARA UN MEJOR DESARROLLO DE SUS NEGOCIOS. R. TRANSIGIR, DESISTIR O SOMETER A DECISIONES ARBITRALES LAS CUESTIONES EN QUE TENGA INTERES FRENTE A TERCEROS. ; S. SOLICITAR, CONSEGUIR LOS REGISTROS RESPECTIVOS ANTE LA AUTORIDAD COMPETENTE Y EXPLOTAR EL DERECHO SOBRE MARCAS, NOMBRES COMERCIALES O CUALQUIER SIGNO DISTINTIVO, DIBUJOS, INSIGNIAS, PATENTES Y CUALQUIER OTRO DERECHO DE PROPIEDAD INDUSTRIAL O INTELECTUAL YA SEA A NOMBRE DE LA SOCIEDAD O DE UN TERCERO. T. HACER PUBLICACIONES Y COMUNICACIONES RELACIONADAS CON EL OBJETO SOCIAL. U. CELEBRAR Y EJECUTAR CON SU PROPIO NOMBRE Y POR CUENTA DE TERCEROS O EN PARTICIPACION CON ELLOS, ACTOS O CONTRATOS Y OPERACIONES EN GENERAL, TODO ACTO O CONTRATO QUE SEA NECESARIO O CONVENIENTE PARA CUMPLIR O FACILITAR LOS ACTOS Y OPERACIONES PREVISTAS EN LOS ESTATUTOS Y QUE DE MANERA DIRECTA SE RELACIONEN CON EL OBJETO SOCIAL, TAL COMO QUEDA DETERMINADO.

CERTIFICA :

CAPITAL Y SOCIOS : $ 120,000,000.00 DIVIDIDO EN 12,000.00 CUOTAS CON VALOR NOMINAL DE $ 10,000.00 CADA UNA, DISTRIBUIDO ASI :

- SOCIOS CAPITALISTA(S)

FRIERI DEL CASTILLO ANA MARIA C.C. 00045483209
NO. CUOTAS: 4,000.00 VALOR:$40,000,000.00
RAISBECK LLINAS JAMES IAN C.C. 00079376996
NO. CUOTAS: 4,000.00 VALOR:$40,000,000.00
OLARTE GARCIA CARLOS REINALDO C.C. 00079782747
NO. CUOTAS: 4,000.00 VALOR:$40,000,000.00
TOTALES
NO. CUOTAS: 12,000.00 VALOR :$120,000,000.00

CERTIFICA :

REPRESENTACION LEGAL : LA SOCIEDAD TENDRA UN GERENTE GENERAL, EL CUAL TENDRA UN PRIMER SUPLENTE Y UN SEGUNDO SUPLENTE QUE LO

REEMPLAZARA EN SUS FALTAS ABSOLUTAS, TEMPORALES O ACCIDENTALES, Y CUYA DESIGNACION Y REMOCION CORRESPONDERA TAMBIEN A LA JUNTA DE SOCIOS.

CERTIFICA :

** NOMBRAMIENTOS : **

QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

| NOMBRE | IDENTIFICACION |
|---|---|
| GERENTE | |
| OLARTE GARCIA CARLOS REINALDO | C.C.00079782747 |
| PRIMER SUPLENTE DEL GERENTE | |
| RAISBECK LLINAS JAMES IAN | C.C.00079376996 |
| SEGUNDO SUPLENTE DEL GERENTE | |
| FRIERI DEL CASTILLO ANA MARIA | C.C.00045483209 |

CERTIFICA :

FACULTADES DEL REPRESENTANTE LEGAL : EL GERENTE GENERAL ES EL REPRESENTANTE LEGAL DE LA SOCIEDAD, Y EN CASO DE FALTA TEMPORAL O ABSOLUTA HARA SUS VECES EL PRIMER SUPLENTE O EN SU DEFECTO EL SEGUNDO SUPLENTE, TAMBIEN ELEGIDOS POR LA JUNTA DE SOCIOS. EL GERENTE REPRESENTARA Y COMPROMETERA A LA SOCIEDAD FRENTE A TERCEROS, SEAN PERSONAS O ENTIDADES PARTICULARES, OFICIALES O JUDICIALES. ASI MISMO, PODRA CELEBRAR EN SU NOMBRE CONTRATO DE ARRENDAMIENTO COMO ARRENDADOR O ARRENDATARIO. CONSTITUIR APODERADOS DE LA SOCIEDAD, DESISTIR, INTERPONER TODA CLASE DE RECURSOS RECIBIR DINERO EN MUTUO, HACER DEPOSITOS BANCARIOS O DE CUALQUIER OTRA INDOLE, FIRMAR TITULOS VALORES Y NEGOCIARLOS, TENERLOS, CONTRATARLOS, PAGARLOS, ENDOSARLOS, DESCARGARLOS, CELEBRAR CONTRATOS COMERCIALES, EJECUTAR LOS ACUERDOS DE LA JUNTA DE SOCIOS Y CONVOCARLA A REUNIONES ORDINARIAS O EXTRAORDINARIAS, SUSCRIBIR CONTRATOS LABORALES A NOMBRE DE LA SOCIEDAD, Y EN GENERAL TODAS LAS GESTIONES QUE OBEDEZCAN A LA NATURALEZA DE SU ENCARGO Y QUE SE RELACIONEN DIRECTAMENTE CON EL GIRO ORDINARIO DE LOS NEGOCIOS SOCIALES. EL GERENTE REQUERIRA APROBACION DE LA JUNTA DE SOCIOS PARA CELEBRAR ACTOS CUYA CUANTIA SEA O EXCEDA LA SUMA DE DIEZ MILLONES DE PESOS ($10,000,000) MONEDA CORRIENTE.

CERTIFICA :

** REVISOR FISCAL: **

QUE POR ACTA NO. 0000006 DE JUNTA DE SOCIOS DEL 5 DE MARZO DE 2004 , INSCRITA EL 8 DE JULIO DE 2004 BAJO EL NUMERO 00942232 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

| NOMBRE | IDENTIFICACION |
|---|---|
| REVISOR FISCAL | |
| LACHE NUÑEZ JOSE LUCIO | C.C.00006763005 |

CERTIFICA :

DIRECCION DE NOTIFICACION JUDICIAL : CLL 100 NO 8A-37 P 10 W.T.C.

María Eugenia Rojas de Urrea

T A
MUNICIPIO : BOGOTA D.C.
DIRECCION COMERCIAL : CLL 100 NO 8A-37 P 10 W.T.C. T A
MUNICIPIO : BOGOTA D.C.
E-MAIL : ELIZABETH.BARBOSA@OLARTERAISBECK.COM

CERTIFICA :

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS :
NOMBRE : OR LEGAL LIMITADA
MATRICULA NO. 01284255
RENOVACION DE LA MATRICULA : EL 27 DE MARZO DE 2006
ULTIMO AÑO RENOVADO : 2006

CERTIFICA :

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

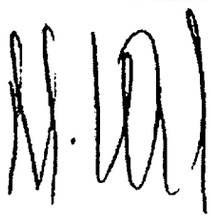
INFORMACION COMPLEMENTARIA

LOS SIGUIENTES DATOS SOBRE RIT Y PLANEACION DISTRITAL SON INFORMATIVOS
CONTRIBUYENTE INSCRITO EN EL REGISTRO RIT DE LA DIRECCION DISTRITAL DE IMPUESTOS, FECHA DE INSCRIPCION 2003/06/24
FECHA DE ENVIO DE INFORMACION A PLANEACION DISTRITAL: 10 DE JULIO DE 2004

EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : $ 3,000.00

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.



TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

*El documento de Poder de Merck & Co., Inc. a Olarte Raisbeck & Frieri Ltda. lleva una certificación notarial con el siguiente sello en inglés:*

(Firmado)

Sello: "Barbara Ann Cozzi, Notario Público de New Jersey – Mi comisión vence el 30 de Noviembre de 2008".

MINISTERIO DE RELACIONES EXTERIORES
573217
COTEJADA PARCIALMENTE
DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

*Apostilla adjunta:*

APOSTILLA:

(Convention de La Haye du 5 octobre 1961)

| | |
|---|---|
| 1. País: | Estados Unidos de Amé |
| | El presente documento público |
| 2. Ha sido firmado por: | Barbara Ann Cozzi |
| 3. Actuando en calidad de: | Notario Público de New Jersey |
| 4. Lleva el sello/estampilla de: | Barbara Ann Cozzi, Notario |
| | Certificado |
| 5. En: | Trenton, New Jersey |
| 6. El: | 6 de February de 2007 |
| 7. Por: | Bradley Abelow, Tesorero de New Jersey |
| 8. Bajo el No.: | A282565 |
| 9. Sello / estampilla: | El Estado de New Jersey – Sello del Estado |
| 10. Firma: | Bradley Abelow |

2007 MAR 1 A 8:49
JEFE DE LEGALIZACIONES BOGOTA D.C.
NO SE ASUME RESPONSABILIDAD DEL TEXTO

María Cristina Sánchez Mejía

Traductor Oficial
JORGE E. SIERRA REYES
Decreto 376 - 1993 Minjusti

*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Merck & Co.Inc. - Apost."*

*Fecha: 15 de Febrero de 2007.*

*Traductor: Jorge Enrique Sierra Reyes.*

*Licencia No. 376 de 1993, del Ministerio de Justicia.*

*Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.*

*Teléfono: (57-1) 2182308, (57-1) 6232925.*

*E-mail: treseser1@yahoo.com. No. 9508*

Traductor Oficial
JORGE E. SIERRA REYES
...encia 376 - 1993 Minjusticia

10

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA ANN COZZI

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
BARBARA ANN COZZI, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

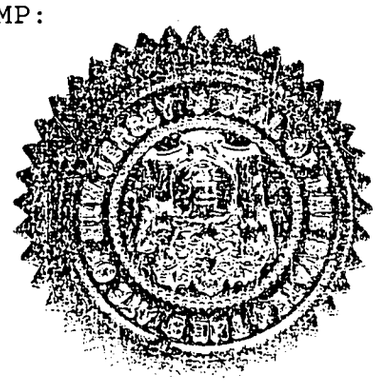
6. THE 6TH DAY OF FEBRUARY 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A282565

9. SEAL/STAMP:

10. SIGNATURE



Bradley Abelow

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
José Luis Londoño
Felipe Mendoza
Simón Salinas
Alexander Agudelo
Camilo A. Rodríguez

Of Counsel
Guillermo Chahin
Graciela Melo
Jacqueline Chaparro
Cruz E. de Moncaleano

# General Power

The undersigned,

domiciled in

hereby appoint Olarte Raisbeck & Frieri Ltda. with offices in the World Trade Center – Torre A, Calle 100 No. 8A-37, Piso 10, Bogota D.C., legal representatives with authority to receive notifications and to appoint judicial or extrajudicial agents in patent matters, who at the same time have the authority to represent us before the administrative, judicial or police authorities of any hierarchy of the Republic of Colombia, the Republic of Bolivia, the Republic of Ecuador, the Republic of Peru, and the Bolivarian Republic of Venezuela, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to draw up specifications; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

# Poder General

El suscrito,

MERCK & CO., INC.

domiciliado en

126 EAST LINCOLN AVENUE, RAHWAY, NJ 07065-0907, USA.

nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con oficinas en el World Trade Center – Torre A, Calle 100 No. 8A-37, Piso 10, Bogotá D.C., nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

Signature/Firma:X Donna L. Margiotto

Donna L. Margiotto, Senior Manager, Patent Administration

Date/Fecha: February 1, 2007

City,Country/Ciudad,País: Rahway, NJ, USA.

## MODEL OF NOTARIAL CERTIFICATION

| **Notarial Certification** | **Certificación Notarial** |
|---|---|
| On this date, February 1, 2007 | En esta fecha, |
| The undersigned Notary Public certifies: | el Notario Público suscrito certifica: |
| 1. That | 1. Que |
| Donna L. Margiotto | |
| of legal age and domiciled in | mayor de edad y domiciliado |
| 126 East Lincoln Avenue, Rahway, NJ 07065-0907, USA. | |
| signed the foregoing document. | suscribió el documento que antecede. |
| 2. That the grantor has executed the foregoing document as Senior Manager, Patent Administration of MERCK & CO., INC. | 2. Que el otorgante ha suscrito el referido documento en su carácter de<br><br>de |
| 3. That MERCK & CO., INC., having its principal place of business located in New Jersey, USA. is duly incorporated, is currently in existence, and that the purposes for which the General Power is granted are within the scope of its corporate purposes. | 4. Que<br>con sede principal ubicada en<br><br>está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social. |
| 4. That the grantor has the authority to execute the General Power and that his/her representation is legal. | 4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima. |
| 5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s): Corporate Resolution No. 5 – Patent Matters, amended October 24, 2006 by the Board of Directors of Merck & Co., Inc. at a meeting held on October 24, 2006. | 5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s): |

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueta

NOTARY PUBLIC (Signature):X Barbara Ann Cozzi

**BARBARA ANN COZZI**
**Notary Public of New Jersey**
**My Commission Expires Nov. 30, 2008**

ESTA HOJA EN BLANCO

WK 4682370

Aministration. ----------

Fecha febrero 2007 ----------

Ciudad País: Rahway, NJ, USA----------

CERTIFICACION NOTARIAL .----------

En esta fecha, ----------

El notario público suscrito certifica: ------

1. Que Donna L. Margiotto mayor de edad, y domiciliado 126 East Lincoln Avenue, Rahway, NJ 07065-0907, USA. Suscribió el documento que antecede. ----------

2. Que el otorgamiento ha suscrito el referido documento en su carácter de de ----------

4. Que ----------

con sede principal ubicada en ----------

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentran dentro de los que comprenden su objeto social.----------

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legitima. ----------

5. El fundamento de mis certificaciones contenidas en los puntos 2,3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s): ----------

NOTARIA VEINTISIETE María Eugenia Ospina de Orueta

NOTARY PUBLIC (fdo. ilegible) BARBARA ANN COZZI Notary Public Of New Jersey My Comisión Expires Nov. 30, 2006 --------

TRADUCCION OFICIAL DE UN DOCUMENTO QUE ESTA ORIGINALMENTE EN INGLES ----------

El documento de Poder de Merck & Co., Inc. a Olarte Raisbeck & Frieri Ltda. lleva una certificación notarial con el siguiente sello en inglés:----------

(Firmado) ----------

Sello: " Barbara Ann Cozzi, Notario Público de New Jersey- Mi comisión vence el 30 de Noviembre de 2008".----------

APOSTILLA

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

(Convention de La Haye Du 5 octobre 1961)

1. País: Estados Unidos de América ----------

El presente documento público ----------

2. Ha sido firmado por: Barbara Ann Cozzi----

3. Actuando en calidad de: Notario Público de New Jersey.--------

4 Lleva el sello/ estampilla de: Barbara Ann Cozzi, notario ------

Certificado

5. En: Trenton, New Jersey} ----------

6) El 6 de February de 2007 ----------

7. Por: Bradley Abelow, Tesorero de New Jesery. ----------

8 Bajo el No. A282565 ----------

9. Sello/ estampilla: El Estado de New Jesery- Sello del Estado--

10. Firma: Bradley Abelow ----------

Certificación: ----------

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Merck & Co. Inc.- Apost"----------

Fecha: 15 de Febrero de 2007.----------

Traductor: Jorge Enrique Sierra Reyes.- ----------

Licencia No. 376 de 1993, del Ministerio de Justicia.- ----------

Dirección Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia. ---

Teléfono: (57-1) 2182308, (57-1) 6232925.- ----------

E-mail: treseser1@yahoo.com 9508- ----------

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dicho documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten ----------

---

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El(los) compareciente(s) hace(n) constar que han verificado cuidadosamente sus nombres completos, estado(s) civil(es), los número(s) de sus documentos de identidad; Declara(n) que todas las informaciones consignadas en el presente instrumento son correctas y, en consecuencia, asumen la responsabilidad que

WK 4682371

se derive de cualquier inexactitud en los mismos. Conocen la ley y saben que el Notario responde de la regularidad formal de los instrumentos que autoriza, pero no de la veracidad de las declaraciones de los interesados.

ADVERTENCIA, OTORGAMIENTO Y AUTORIZACION.- Leído el presente instrumento por el (los) compareciente (s) y advertido (s) sobre las formalidades legales, lo aprueban y firman conmigo y ante mí la(el) Notaria(o) quién lo autoriza. A los otorgantes se les advirtió finalmente que una vez firmado el presente instrumento, La(el) Notaria(o) no aceptará correcciones o modificaciones sino en la forma y casos previstos por la Ley. ---Se utilizaron las hojas de papel Notarial Nos : WK 4682369, WK 4682370, WK 4682371.- - - - - - - - - - - - - - - - -

NOTARIA VEINTISIETE
María Eugenia Rojas de Uribe

DERECHOS LEGALES: $ 38.110.oo
RESOLUCION 7880 DE 2006
IVA $ 14.642.oo

CARLOS REINALDO OLARTE GARCIA
C.C.No. 79'782.747 Bogotá
TEL: 601-7700

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

MARIA EUGENIA ROJAS DE URUETA

NOTARIA(O) VENTISIETE (27) DE BOGOTA

REPUBLICA DE COLOMBIA
27
María Eugenia Rojas
de Urueta
NOTARIa
Notaría Veintisiete de Santafé de Bogotá

redb.

Es fiel y Segunda (2ª)
fotocopia de la Escritura Pública No. 812
de fecha 22 de Marzo de 2001
tomada de su original que expido en
Ocho ( 8 ) hojas útiles de papel
común autorizado (Decreto1348 de 1970) con destino a
Interesado

Dado en Santafé de Bogotá D.C., a 29 MAR. 2001
El Notario Veintisiete de Santafé de Bogotá,

REPUBLICA DE COLOMBIA
27
María Eugenia Rojas
de Urueta
NOTARIa
Notaría Veintisiete de Santafé de Bogotá

ESTA HOJA EN BLANCO

**Caso de Patente: MS0063Y**

# APOSTILLA

## (CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: ESTADOS UNIDOS DE AMERICA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR: BARBARA ANN COZZI
3. EN CALIDAD DE: NOTARIO PÚBLICO
4. CERTIFICADO CON EL SELLO DE: BARBARA ANN COZZI, NOTARIO PÚBLICO

CERTIFICO

5. EN TRENTON. NEW JERSEY
6. EL 21 DE NOVIEMBRE DEL 2007
7. POR: Michelene Davis, TESORERA DE NEW JERSEY
8. No. A309652
9. SELLO: DEL ESTADO DE NEW JERSEY
10. FIRMA: (ILEGIBLE)

**Caso de Patente: MS0063Y**

**ESTADO DE NEW JERSEY )**
**) SS:**
**CONDADO DE LA UNION )**

**YO, VERONICA BARONE,** por este medio juro que las fotocopias adjuntas de: U. S. Cesiones y acuerdos, Caso número **MS0063Y,** titulado **INHIBIDORES DE ACTIVIDAD AKT,** son verdaderos, correctos, y copias completas de los documentos originales de las cuales yo tengo la responsabilidad y la custodia.

Firma: Verónica Barone
**VERONICA BARONE**
**EMPLEADA DE PLANTA II**

Firma y jura ante mí el 21 de Septiembre de 2007

Firma: Bárbara Ann Cozzi
**NOTARIA PÚBLICA**

**BARBARA ANN COZZI**
**Notaria Pública de New Jersey**
"Mi comisión expira el 30 de Noviembre de 2008"

Caso Extranjero #: MS 0063Y

**Caso de Patente: MS0063Y**

# CESIÓN Y ACUERDO

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

1. Donna J.Armstrong, 2. Michael J. Kelly, Iii, 3. Mark E. Layton, 4. Kevin J. Rodzinak, 5. Michael A. Rossi, 6. Philip E. Sanderson, 7. Jiabing Wang.

Domiciliados respectivamente en

(1) 570 Meetinghouse Road, Harleysville, Pennsylvania 19438 ;

(2) 319 Drummers Lane, Wayne, Pennsylvania 19087 ;

(3) 73 Astor Drive, Harleysville, Pennsylvania 19438 ;

(4) 103 Eaglet Lane, Schwenksville, Pennsylvania 19473 ;

(5) 156 Jordan Court, Limerick, Pennsylavnia 19468 ;

(6) 10 Jug Hallow Road, Valley Forge, Pennsylvania 19481 ; y

(7) 502 Basset Court, Chalfont, Pennsylvania 18914 ; respectivamente,

Por medio de la presente vendemos y transferimos a MERCK &CO., Inc., una corporación del Estado de New Jersey, la cual tiene su dirección comercial en la Avenida Lincoln, en la ciudad de Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, en y por cierto invento relacionado a

# INHIBIDORES DE ACTIVIDAD AKT

Descrito en una solicitud de Patentes teniendo como número asignado MS0063Y y con número serial de solicitud 60/689,726 presentado el 06 de Octubre de 2005; Número de Serial 60/734,188 presentado el 07 de Noviembre de 2005 en y para todos nuestros derechos y privilegios incluyendo cualquier y todos los beneficios bajo la Convención Internacional Para la Protección de la Propiedad Industrial, bajo cualquier y todas las Patentes que puedan ser otorgadas en el futuro, y bajo cualquier y todas las extensiones, divisionales, re-otorgamientos y continuaciones de dicha solicitud de Patentes, incluyendo cualquier solicitud extranjera derivada de esta, equivalente a esta o reclamo prioridad a esta.

Solicitamos que cualquier y todas las Patentes por dichos inventos sean otorgados a dicho asignado, sus sucesores, asignados y representantes legales, o a los nominados a quien desee asignar el designado.

Estamos de acuerdo que, cuando sea necesario, nosotros, al requerirse, pero a expensas del cesionario, firmaremos todos los papeles, realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para asegurar y mantener las Patentes de dichos inventos en cualquier y en todos los países y por el título descrito y por el designado expresado en este, sus sucesores, asignados y representantes legales o nominados.

Nosotros acordamos con dicho ASIGNADO, sus sucesores, asignados y representantes legales, que los derechos y propiedad aquí transmitidos están libres y claros de cualquier obstáculo, y que poseemos el total derecho para transmitir el mismo como se ha expresado en este.

Este documento puede ser ejecutado en cualquier número de homólogos, los cuales al ser ejecutados deben ser aceptados como un original, pero todos y cada homólogo deben ser constituir juntos uno solo del mismo documento.

Nosotros por este medio autorizamos nuestro abogado representante, Mathew A. Leff o a un Abogado Apoderado en esta solicitud, de la mencionada MERCK & CO., Inc., para insertar el serial número(s), PCT solicitud número y fecha(s) de presentación de dicha solicitud cuando lo sepamos.

Firmado en West Point, Pennsylvania el 24 de Mayo del 2006

Firma ilegible: _____
Michael J. Nelly, III

Firma ilegible: _____
Mark E. Layton

Firma ilegible: _____
Kevin J. Rodzinak

Firma ilegible: _____
Michael A. rossi

Firma ilegible: _____
Philip E. Sanderson

ESTADO DE PENNSYLVANIA

} SS.

Condado de Montgomery

Personalmente se presentaron ante mi los arriba mencionados: Donna J.Armstrong, Michael J. Kelly, Iii, Mark E. Layton, Kevin J. Rodzinak, Michael A. Rossi, Philip E. Sanderson, Jiabing Wang.

Quienes demostraron ante mi ser las personas que ejecutaron el presente documento y reconocen que dicho instrumento es elaborado por su propia voluntad y certifican este mismo el 24 de Mayo de 2006.

Firma ilegible

Notaria Pùblica.

Sello Notarial
Marjorie M. Bennett, Notaria Publica
Upper Gwynedd township, Condado de Montgomery
Mi comision expira el 24 de Enero de 2007
Miembro de la Asociacion de Notarios de Pennsylvania

Firmado en West Point, Pennsylvania el 25 de Mayo del 2006

Firma ilegible:

Donna J. Armstrong

Firma ilegible:

Jiabing Wang

ESTADO DE PENNSYLVANIA

} SS.

Condado de Montgomery

Personalmente se presentaron ante mí los arriba mencionados: Quienes demostraron ante mí ser las personas que ejecutaron el presente documento y reconocen que dicho instrumento es elaborado por su propia voluntad y certifican este mismo el 25 de Mayo de 2006.

Firma ilegible

Notaria Pùblica.

Sello Notarial
Marjorie M. Bennett, Notaria Publica
Upper Gwynedd township, Condado de Montgomery
Mi comision expira el 24 de Enero de 2007
Miembro de la Asociacion de Notarios de Pennsylvania

20

# CESIÓN Y ACUERDO

Por buena y onerosa consideración, del cual se acusa recibo suficiente, yo

1. Yiwei Li

Domiciliado en

11632 Miro Circle, San Diego, California 92131

Por medio de la presente vendo y transfiero a MERCK & CO., Inc., una corporación del Estado de New Jersey, la cual tiene su dirección comercial en la Avenida Lincoln, en la ciudad de Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, en y por cierto invento relacionado a

## INHIBIDORES DE ACTIVIDAD AKT

Descrito en una solicitud de Patentes teniendo como número asignado MS0063Y y con número serial de solicitud 60/689,726 presentado el 06 de Octubre de 2005; Número de Serial 60/734,188 presentado el 07 de Noviembre de 2005 en y para todos mis derechos y privilegios incluyendo cualquier y todos los beneficios bajo la Convención Internacional Para la Protección de la Propiedad Industrial, bajo cualquier y todas las Patentes que puedan ser otorgadas en el futuro, y bajo cualquier y todas las extensiones, divisionales, re-otorgamientos y continuaciones de dicha solicitud de Patentes, incluyendo cualquier solicitud extranjera derivada de esta, equivalente a esta o reclamo prioridad a esta.

Solicito que cualquier y todas las Patentes por dichos inventos sean otorgados a dicho asignado, sus sucesores, asignados y representantes legales, o a los nominados a quien desee asignar el designado.

Estoy de acuerdo que, cuando sea necesario, yo, al requerirse, pero a expensas del cesionario, firmaré todos los papeles, realizaré las declaraciones necesarias juramentadas y realizaré todos los actos jurídicos necesarios para asegurar y mantener las Patentes de dichos inventos en cualquier y en todos los países y por el título descrito y por el designado expresado en este, sus sucesores, asignados y representantes legales o nominados.

Yo acuerdo con dicho ASIGNADO, sus sucesores, asignados y representantes legales, que los derechos y propiedad aquí transmitidos están libres y claros de cualquier obstáculo, y que poseo el total derecho para transmitir el mismo como se ha expresado en este.

Este documento puede ser ejecutado en cualquier número de homólogos, los cuales al ser ejecutados deben ser aceptados como un original, pero todos y cada homólogo deben ser constituir juntos uno solo del mismo documento.

Yo por este medio autorizo a mi abogado representante, Mathew A. Leff o a un Abogado Apoderado en esta solicitud, de la mencionada MERCK & CO., Inc., para insertar el serial número(s), PCT solicitud número y fecha(s) de presentación de dicha solicitud cuando lo sepa.

Firmado en San Diego, California el 01 de Junio de 2006

Firma ilegible:
Yiwei Li

ESTADO DE CALIFORNIA

} SS.

Condado de SAN DIEGO

Personalmente se presentaron ante mí el arriba mencionado: Quien demostro ante mí ser la persona que ejecuto el presente documento y reconoce que dicho instrumento es elaborado por su propia voluntad y certifica este mismo el 01 de Junio de 2006.

Firma ilegible
Notaria Pùblica.

Sello Notarial
CATHARINE STUHLER
Nùmero de Comision 1428653
Notaria Publica - California
Condado de San Diego
Mi comision expira el 01 de Agosto de 2007

# CESIÓN Y ACUERDO

Por buena y onerosa consideración, del cual se acusa recibo suficiente, yo

1. Jung Liang

Domiciliado en

557 Driscoll Place, Palo Alto, California 94306

Por medio de la presente vendo y transfiero a MERCK & CO., Inc., una corporación del Estado de New Jersey, la cual tiene su dirección comercial en la Avenida Lincoln, en la ciudad de Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, en y por cierto invento relacionado a

# INHIBIDORES DE ACTIVIDAD AKT

Descrito en una solicitud de Patentes teniendo como número asignado MS0063Y y con número serial de solicitud 60/689,726 presentado el 06 de Octubre de 2005; Número de Serial 60/734,188 presentado el 07 de Noviembre de 2005 en y para todos mis derechos y privilegios incluyendo cualquier y todos los beneficios bajo la Convención Internacional Para la Protección de la Propiedad Industrial, bajo cualquier y todas las Patentes que puedan ser otorgadas en el futuro, y bajo cualquier y todas las extensiones, divisionales, re-otorgamientos y continuaciones de dicha solicitud de Patentes, incluyendo cualquier solicitud extranjera derivada de esta, equivalente a esta o reclamo prioridad a esta.

Solicito que cualquier y todas las Patentes por dichos inventos sean otorgados a dicho asignado, sus sucesores, asignados y representantes legales, o a los nominados a quien desee asignar el designado.

Estoy de acuerdo que, cuando sea necesario, yo, al requerirse, pero a expensas del cesionario, firmaré todos los papeles, realizaré las declaraciones necesarias juramentadas y realizaré todos los actos jurídicos necesarios para asegurar y mantener las Patentes de dichos inventos en cualquier y en todos los países y por el título descrito y por el designado expresado en este, sus sucesores, asignados y representantes legales o nominados.

Yo acuerdo con dicho ASIGNADO, sus sucesores, asignados y representantes legales, que los derechos y propiedad aquí transmitidos están libres y claros de cualquier obstáculo, y que poseo el total derecho para transmitir el mismo como se ha expresado en este.

Este documento puede ser ejecutado en cualquier número de homólogos, los cuales al ser ejecutados deben ser aceptados como un original, pero todos y cada homólogo deben ser constituir juntos uno solo del mismo documento.

Nosotros por este medio autorizamos nuestro abogado representante, Mathew A. Leff o a un Abogado Apoderado en esta solicitud, de la mencionada MERCK & CO., Inc., para insertar el serial número(s), PCT solicitud número y fecha(s) de presentación de dicha solicitud cuando lo sepamos.

Firmado en Palo Alto, California el 27 de Mayo de 2006

Firma ilegible:
Jun Liang

ESTADO DE CALIFORNIA

} SS.

Condado de SANTA CLARA

Personalmente se presento ante mí el arriba mencionado Jun Liang: Quien demostro ante mí ser la persona que ejecuto el presente documento y reconoce que dicho instrumento es elaborado por su propia voluntad y certifica este mismo el 27 de Mayo de 2006.

Firma ilegible
Notaria Pùblica.

Sello Notarial
KAREN CHOY SINGER
Nùmero de Comision 1378863
Notaria Publica - California
Condado de San Mateo
Mi comision expira el 07 de Octubre de 2006

# CESIÓN Y ACUERDO

Por buena y onerosa consideración, del cual se acusa recibo suficiente, yo

1. Essa H. Hu

Domiciliado en

3824 Fountain Street, Camarillo, California 93012

Por medio de la presente vendo y transfiero a MERCK & CO., Inc., una corporación del Estado de New Jersey, la cual tiene su dirección comercial en la Avenida Lincoln, en la ciudad de Rahway, Estado de New Jersey, y sus sucesores, cesionarios y representantes legales todos mis derechos titulo e interés para todos los países del mundo, en y por cierto invento relacionado a

## INHIBIDORES DE ACTIVIDAD AKT

Descrito en una solicitud de Patentes teniendo como número asignado MS0063Y y con número serial de solicitud 60/689,726 presentado el 06 de Octubre de 2005; Número de Serial 60/734,188 presentado el 07 de Noviembre de 2005 en y para todos mis derechos y privilegios incluyendo cualquier y todos los beneficios bajo la Convención Internacional Para la Protección de la Propiedad Industrial, bajo cualquier y todas las Patentes que puedan ser otorgadas en el futuro, y bajo cualquier y todas las extensiones, divisionales, re-otorgamientos y continuaciones de dicha solicitud de Patentes, incluyendo cualquier solicitud extranjera derivada de esta, equivalente a esta o reclamo prioridad a esta.

Solicito que cualquier y todas las Patentes por dichos inventos sean otorgados a dicho asignado, sus sucesores, asignados y representantes legales, o a los nominados a quien desee asignar el designado.

Estoy de acuerdo que, cuando sea necesario, yo, al requerirse, pero a expensas del cesionario, firmaré todos los papeles, realizaré las declaraciones necesarias juramentadas y realizaré todos los actos jurídicos necesarios para asegurar y mantener las Patentes de dichos inventos en cualquier y en todos los países y por el título descrito y por el designado expresado en este, sus sucesores, asignados y representantes legales o nominados.

Yo acuerdo con dicho ASIGNADO, sus sucesores, asignados y representantes legales, que los derechos y propiedad aquí transmitidos están libres y claros de cualquier obstáculo, y que poseo el total derecho para transmitir el mismo como se ha expresado en este.

Este documento puede ser ejecutado en cualquier número de homólogos, los cuales al ser ejecutados deben ser aceptados como un original, pero todos y cada homólogo deben ser constituir juntos uno solo del mismo documento.

Yo por este medio autorizo mi abogado representante, Mathew A. Leff o a un Abogado Apoderado en esta solicitud, de la mencionada MERCK & CO., Inc., para insertar el serial número(s), PCT solicitud número y fecha(s) de presentación de dicha solicitud cuando lo sepa.

Firmado en Camarillo, California el 03 de Junio de 2006

Firma ilegible:
Essa H. Hu

ESTADO DE CALIFORNIA

} SS.

Condado de VENTURA

Personalmente se presento ante mí el arriba mencionado Essa H. Hu: Quien demostro ante mi ser la persona que ejecuto el presente documento y reconoce que dicho instrumento es elaborado por su propia voluntad y certifica este mismo el 03 de Junio de 2006.

Firma ilegible
Notaria Pùblica.

Sello Notarial
LINDA SANTANA
Nùmero de Comision 1654742
Notaria Publica - California
Condado de Ventura
Mi comision expira el 28 de Marzo de 2010

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA ANN COZZI

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
BARBARA ANN COZZI, NOTARY

CERTIFIED

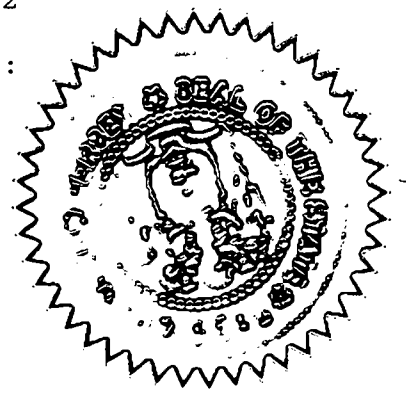
5. AT TRENTON, NEW JERSEY

6. THE 21ST DAY OF NOVEMBER 2007

7. BY: Michellene Davis, NEW JERSEY TREASURER

8. NO. A309652

9. SEAL/STAMP:



10. SIGNATURE

COLOMBIA

**STATE OF NEW JERSEY )**
**) SS:**
**COUNTY OF UNION )**

I, **VERONICA BARONE**, hereby swear that the attached photocopies of:

U.S. Assignments and Agreements, Case No. MS0063Y, entitled INHIBITORS OF AKT ACTIVITY, are true, correct, and complete copies of the original documents for which I have custodial responsibility.

Veronica Barone

**VERONICA BARONE**
**STAFF ASSOCIATE II**

Subscribed and sworn to before me this 21st day of September, 2007.

Barbara Ann Cozzi

**NOTARY PUBLIC**

**BARBARA ANN COZZI**
**Notary Public of New Jersey**
**My Commission Expires Nov. 30, 2008**

Foreign Case No.: MS0063Y

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

For value received, we, Donna J. Armstrong, Michael J. Kelly, III, Mark E. Layton, Kevin J. Rodzinak, Michael A. Rossi, Philip E. Sanderson, Jiabing Wang

of 570 Meetinghouse Road, Harleysville, Pennsylvania 19438;
319 Drummers Lane, Wayne, Pennsylvania 19087;
73 Astor Drive, Harleysville, Pennsylvania 19438;
103 Eaglet Lane, Schwenksville, Pennsylvania 19473;
156 Jordan Court, Limerick, Pennsylvania 19468;
10 Jug Hallow Road, Valley Forge, Pennsylvania 19481;
502 Basset Court, Chalfont, Pennsylvania 18914; respectively,

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, our entire right, title and interest, for all countries, in and to certain inventions relating to

INHIBITORS OF AKT ACTIVITY

described in an application for Patents having Attorney Docket Number MS0063Y and in application(s) Serial No. 60/689,726 filed on 06/10/2005 ; Serial No. 60/734,188 filed on 11/07/2005 ; Serial No. filed on (if applicable),

and all our rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, under any and all Patents which may be granted therefor, and under any and all extensions, divisionals, reissues and continuations of said application for Patents, including any foreign applications derived therefrom, equivalent thereto or claiming priority thereof.

We request that any and all Patents for said inventions be issued to said assignee, its successor, assigns and legal representatives, or to such nominees as it may designate.

We agree that, when requested, we will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

We covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that we have full right to convey the same as herein expressed.

This document may be executed in any number of counterparts, each of which so executed shall be deemed to be an original, but all such counterparts shall together constitute but one and the same document.

We hereby authorize our attorney, Matthew A. Leff or an attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert **Serial No. (s), PCT Appl. No. (s)** and **Filing Date (s)** of said application(s) when known.

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

Signed at West Point, Pennsylvania this 24th day of May, 2006.

~~Donna J. Armstrong~~

Michael J. Kelly, III

Mark E. Layton

Kevin J. Rodzinak

Michael A. Rossi

Philip E. Sanderson

~~Jiabing Wang~~

COMMONWEALTH OF PENNSYLVANIA }
County of Montgomery } SS.

Personally appeared before me the above-named Donna J. Armstrong Michael J. Kelly, III Mark E. Layton Kevin J. Rodzinak Michael A. Rossi Philip E. Sanderson Jiabing Wang

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be their free act and deed this 24th day of May, 2006.

Marjorie M. Bennett
*Notary Public*

Notarial Seal
Marjorie M. Bennett, Notary Public
Upper Gwynedd Twp., Montgomery County
My Commission Expires Jan. 24, 2007
Member, Pennsylvania Association Of Notaries

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. 30

Filing Date

PCT Appl. No.

Filing Date

# ASSIGNMENT AND AGREEMENT

Signed at West Point, PA this 25th day of May, 2006.

Donna J Armstrong

Donna J Armstrong

Jiabing Wang

Commonwealth

County of } SS.

Personally appeared before me the above-named

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be

their free act and deed this 25th day of May, 2006.

Marjorie M Bennett

*Notary Public*

Notarial Seal
Marjorie M. Bennett, Notary Public
Upper Gwynedd Twp., Montgomery County
My Commission Expires Jan. 24, 2007
Member, Pennsylvania Association Of Notaries

Signed at West Point, PA this _____ day of _____

County of } SS.

Personally appeared before me the above-named

to me known and known to me to be the person(s) who executed the foregoing instrument and acknowledged said instrument to be

their free act and deed this _____ day of _____, _____.

*Notary Public*

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

For value received, I, Yiwei Li

residing at: 11632 Miro Circle, San Diego, California 92131

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, my entire right, title and interest, for all countries, in and to certain inventions relating to

INHIBITORS OF AKT ACTIVITY

described in an application for Patents having Attorney Docket Number MS0063Y and in application(s) Serial No. 60/689,726 filed on 06/10/2005 ; Serial No. 60/734,188 filed on 11/07/2005 ; Serial No. filed on (if applicable),

and all my rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, under any and all Patents which may be granted therefor, and under any and all extensions, divisionals, reissues and continuations of said application for Patents, including any foreign applications derived therefrom, equivalent thereto or claiming priority thereof.

I request that any and all Patents for said inventions be issued to said assignee, or to its successors, assigns and legal representatives, or to such nominees as it may designate.

I agree that, when requested, I will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

I covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I have full right to convey the same as herein expressed.

I hereby authorize my attorney Matthew A. Leff

o. . attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert the **Serial No. (s)**, **PCT Appl. No. (s)**, and **Filing Date (s)** of said application(s) when known.

Signed at San Diego, California this 1st day of June, 2006.

Yiwei Li

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

STATE OF CALIFORNIA

County of San Diego } SS.

Personally appeared before me the above-named Yiwei Li

to me known and known to me to be the person who executed the foregoing instrument and acknowledged said instrument to be his free act and deed this 1st day of June, 2006.

CATHARINE STUHLER
Commission # 1428653
Notary Public - California
San Diego County
My Comm. Expires Aug 1, 2007

(Catharine) Stuhler

*Notary Public*

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

For value received, I, Jun Liang

residing at: 557 Driscoll Place, Palo Alto, California 94306

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, my entire right, title and interest, for all countries, in and to certain inventions relating to

INHIBITORS OF AKT ACTIVITY

described in an application for Patents having Attorney Docket Number MS0063Y and in application(s) Serial No. 60/689,726 filed on 06/10/2005 ; Serial No. 60/734,188 filed on 11/07/2005 ; Serial No. filed on (if applicable),

and all my rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, under any and all Patents which may be granted therefor, and under any and all extensions, divisionals, reissues and continuations of said application for Patents, including any foreign applications derived therefrom, equivalent thereto or claiming priority thereof.

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I covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I have full right to convey the same as herein expressed.

I hereby authorize my attorney Matthew A. Leff

o. , attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert the **Serial No. (s), PCT Appl. No. (s),** and **Filing Date (s)** of said application(s) when known.

Signed at Palo Alto, CA this 27th day of May, 2006.

Jun Liang

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

STATE OF CALIFORNIA

County of Santa Clara } SS.

Personally appeared before me the above-named Jun Liang

to me ~~known and known~~ proved yes to me to be the person who executed the foregoing instrument and acknowledged said instrument to be his free act and deed this 27th day of May, 2006.

KAREN CHOY SINGER
COMM. #1378863
NOTARY PUBLIC - CALIFORNIA
SAN MATEO COUNTY
My Comm. Expires Oct. 7, 2006

Karen Choy Singer
*Notary Public*

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

For value received, I, Essa H. Hu

residing at: 3824 Fountain Street, Camarillo, California 93012

hereby sell, assign and transfer to MERCK & CO., Inc., a corporation of the State of New Jersey, having an office at Lincoln Avenue, City of Rahway, State of New Jersey, and its successors, assigns and legal representatives, my entire right, title and interest, for all countries, in and to certain inventions relating to

INHIBITORS OF AKT ACTIVITY

described in an application for Patents having Attorney Docket Number MS0063Y and in application(s) Serial No. 60/689,726 filed on 06/10/2005 ; Serial No. 60/734,188 filed on 11/07/2005 ; Serial No. filed on (if applicable),

and all my rights and privileges, including any and all benefits under the International Convention for the Protection of Industrial Property, under any and all Patents which may be granted therefor, and under any and all extensions, divisionals, reissues and continuations of said application for Patents, including any foreign applications derived therefrom, equivalent thereto or claiming priority thereof.

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I agree that, when requested, I will, without charge to said assignee but at its expense, sign all papers, take all rightful oaths, and do all acts which may be necessary, desirable or convenient for securing and maintaining Patents for said inventions in any and all countries and for vesting title thereto in said assignee, its successors, assigns and legal representatives or nominees.

I covenant with said assignee, its successors, assigns and legal representatives, that the rights and property herein conveyed are free and clear of any encumbrance, and that I have full right to convey the same as herein expressed.

I hereby authorize my attorney Matthew A. Leff

or attorney with Power of Attorney in this application, of the said MERCK & CO., Inc., to insert the **Serial No. (s)**, **PCT Appl. No. (s)**, and **Filing Date (s)** of said application(s) when known.

Signed at Camarillo this 3rd day of June, 2006.

Essa H. Hu

PATENT

Attorney Docket Number MS0063Y

U.S. Serial No. _____

Filing Date _____

PCT Appl. No. _____

Filing Date _____

# ASSIGNMENT AND AGREEMENT

STATE OF CALIFORNIA
County of Ventura } SS.

Personally appeared before me the above-named Essa H. Hu

to me known and known to me to be the person who executed the foregoing instrument and acknowledged said instrument to be her free act and deed this 3rd day of June, 2006.

L. SANTANA
Commission # 1654742
Notary Public - California
Ventura County
My Comm. Expires Mar 28, 2010

Linda Santana
*Notary Public*

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2006 (21.12.2006)

PCT

(10) International Publication Number
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*A61K 31/397* (2006.01)

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PCT/US2006/022079

(22) International Filing Date: 7 June 2006 (07.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/689,726 10 June 2005 (10.06.2005) US
60/734,188 7 November 2005 (07.11.2005) US

(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARMSTRONG, Donna, J.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **HU, Essa, H.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **KELLY, Michael, J. III** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LAYTON, Mark, E.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LI, Yiwei** [CA/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **LIANG, Jun** [CN/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **RODZINAK, Kevin, J.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **ROSSI, Michael, A.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **SANDERSON, Philip, E.** [GB/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **WANG, Jiabing** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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

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

**Published:**
— *without international search report and to be republished upon receipt of that report*

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

(54) Title: INHIBITORS OF AKT ACTIVITY

(57) Abstract: The instant invention provides for substituted naphthyridine compounds that inhibit Akt activity. In particular, the compounds disclosed selectively inhibit one or two of the Akt isoforms. The invention also provides for compositions comprising such inhibitory compounds and methods of inhibiting Akt activity by administering the compound to a patient in need of treatment of cancer.

WO 2006/135627 A2

MAL

# PATENT COOPERATION TREATY

WO 2006/135627
PCT/US2006/022079

From the INTERNATIONAL BUREAU

# PCT

NOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATION

To:

MATTHEW LEFF

JAN 04 2007

PATENT DEPARTMENT

MERCK & CO., INC.
126 East Lincoln Avenue
Rahway, NJ 07065-0907
ETATS-UNIS D'AMERIQUE

PAT. REG. COORD.
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MAINTENANCE
CASE REFERENCE CLERK
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MK 11/4/07

| | |
|---|---|
| Date of mailing *(day/month/year)*<br>21 December 2006 (21.12.2006) | |
| Applicant's or agent's file reference<br>PCT MS0063Y | **IMPORTANT NOTICE** |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US2006/022079 | 07 June 2006 (07.06.2006) | 10 June 2005 (10.06.2005) |

Applicant: MERCK & CO., INC. et al

The applicant is hereby **notified** that the International Bureau:

☑ has **published** the above-indicated international application on 21 December 2006 (21.12.2006) under No. WO 2006/135627

☐ has **republished** the above-indicated international application on under No. WO
For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) (*as the case may be*) on the front page of the published international application.

A copy of the international application is available for viewing and downloading on WIPO's website at the following address: http://www.wipo.int/pctdb (under "Query" enter the PCT or WO number).

The applicant may also request a paper copy of the published international application from the International Bureau by submitting a written request to PatentScope@wipo.int or to the address provided below.

RECEIVED
MERCK & CO., INC.
2007 JAN -2 PM 2:24
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| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>Agnes Wittmann-Regis |
| Facsimile No. +41 22 338 82 70 | e-mail: pt06@wipo.int |

Form PCT/IB/311 (April 2006)

TITLE OF THE INVENTION

INHIBITORS OF AKT ACTIVITY

BACKGROUND OF THE INVENTION

The present invention relates to substituted naphthyridine compounds which are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as PKB; hereinafter referred to as "Akt"). The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer.

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-$x_L$, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science*, 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase-1 related proteinases, including caspase-3, caspase-7, caspase-8 and caspase-9 etc (Thornberry et al. *Science*, 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol. Cell. Biol.* 17:1595-1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al., *Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns(3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/threonine kinase Akt, which contains a pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt by upstream kinases. In addition, introduction of constitutively active PI3K or Akt mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Three members of the Akt subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ (hereinafter referred to as "Akt1", "Akt2" and "Akt3"), respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akts are activated by phosphorylation events occurring in response to PI3K signaling. PI3K phosphorylates membrane inositol phospholipids, generating the

second messengers phosphatidyl-inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt. The current model of Akt activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1 occurs on two regulatory sites, $Thr^{308}$ in the catalytic domain activation loop and on $Ser^{473}$ near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2 and Akt3. The upstream kinase, which phosphorylates Akt at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheng *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheng *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol. Chem.* 274:21528-21532 (1999).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would

result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt.

It is also an object of the present invention to provide pharmaceutical compositions that comprise the novel compounds that are inhibitors of Akt.

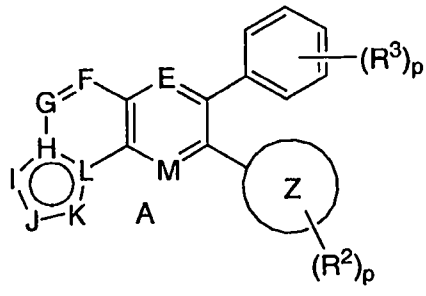
It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt activity.

## SUMMARY OF THE INVENTION

The instant invention provides for substituted naphthyridine compounds that inhibit Akt activity. In particular, the compounds disclosed selectively inhibit one or two of the Akt isoforms. The invention also provides for compositions comprising such inhibitory compounds and methods of inhibiting Akt activity by administering the compound to a patient in need of treatment of cancer.

## DETAILED DESCRIPTION OF THE INVENTION

The compounds of the instant invention are useful in the inhibition of the activity of the serine/threonine kinase Akt. In a first embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula A:




wherein:

E, F, G, H, I, J, K, L and M are independently selected from: C or N, wherein each E, F, G, H, I, J, K, L and M is optionally substituted with $R^1$;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; p is independently 0, 1, 2, 3, 4 or 5;

Ring Z is selected from: ($C_3$-$C_8$)cycloalkyl, aryl, heteroaryl and heterocyclyl;

$R^1$ is selected from: oxo, $(C=O)_aO_b(C_1$-$C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2$-$C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2$-$C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1$-$C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3$-$C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1$-$C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^2$ is independently selected from: oxo, $(C=O)_aO_b(C_1$-$C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2$-$C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2$-$C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1$-$C_6)$perfluoroalkyl,

$(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, SH, $S(O)_mNR^7R^8$, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^3$ is independently selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^6$ is: $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$;

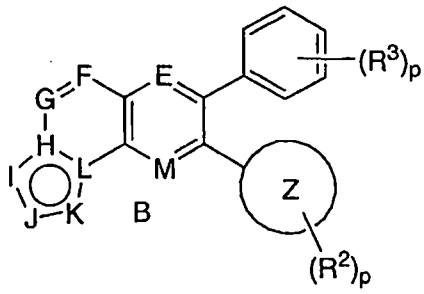
$R^7$ and $R^8$ are independently selected from: H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

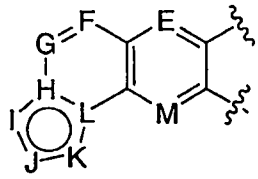
$R^b$ is independently: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C=O)_aO_b(C_1\text{-}C_6)$alkyl, or $S(O)_mR^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

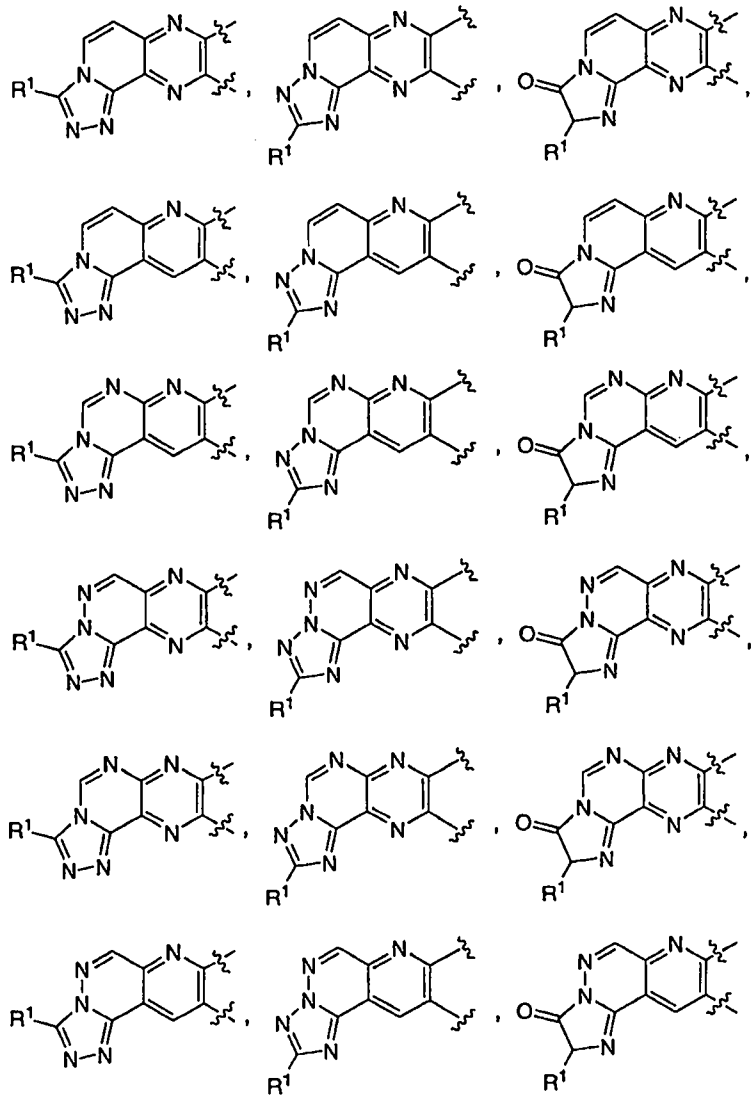
In a second embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula B:



wherein:



is selected from:



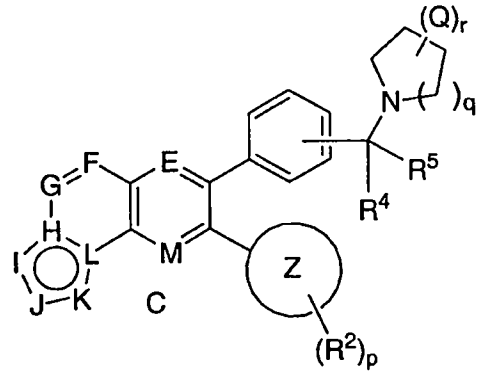
;

$R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

and all other substituents and variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a third embodiment of this invention, the inhibitors of Akt activity are illustrated by the Formula C:



wherein:

q is 0, 1, 2, 3 or 4; r is 0, 1, 2, 3, 4 or 5; t is 2, 3, 4, 5 or 6;

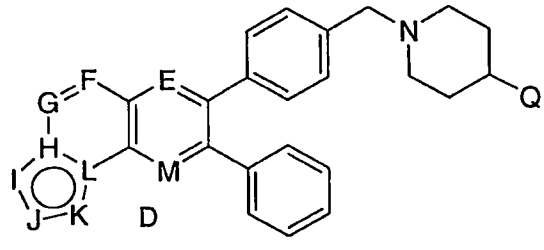
Q is independently selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^{6a}$;

$R^4$ and $R^5$ are independently selected from: H, $(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$perfluoroalkyl, or $R^4$ and $R^5$ are combined to form $-(CH_2)_t-$ wherein one of the carbon atoms is optionally replaced by a moiety selected from O, $S(O)_m$, $-N(R^b)C(O)-$, and $-N(COR^a)-$;

and all other substituents and variables are as defined in the second embodiment;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a fourth embodiment the inhibitors of the instant invention are illustrated by the Formula D:

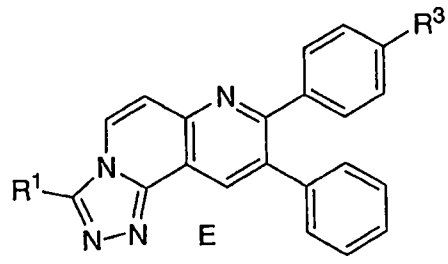


wherein:

all other substituents and variables are as defined in the third embodiment;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a fifth embodiment the inhibitors of the instant invention are illustrated by the Formula E:



E

wherein:

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;

$R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^3$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^6$ is: $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$;

$R^7$ and $R^8$ are independently selected from: H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted

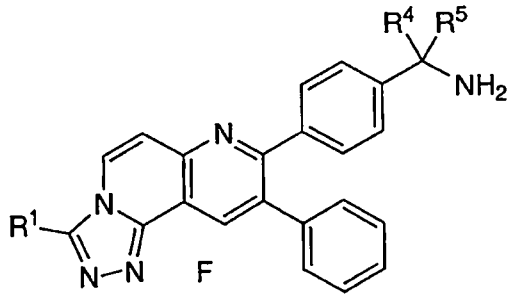
with one or more substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

$R^b$ is independently: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)_a O_b(C_1\text{-}C_6)$alkyl, or $S(O)_m R^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a sixth embodiment the inhibitors of the instant invention are illustrated by the Formula F:




F

wherein:

$R^4$ and $R^5$ are independently: H and $(C_1\text{-}C_6)$alkyl, wherein said alkyl is optionally substituted with up to three substituents selected from: OH and halo; and wherein $R^4$ and $R^5$ may be joined to form a $(C_3\text{-}C_7)$cycloalkyl; and

all other substituents and variables are as defined in the fifth embodiment;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a seventh embodiment the inhibitors of the instant invention are illustrated by the Formula F:

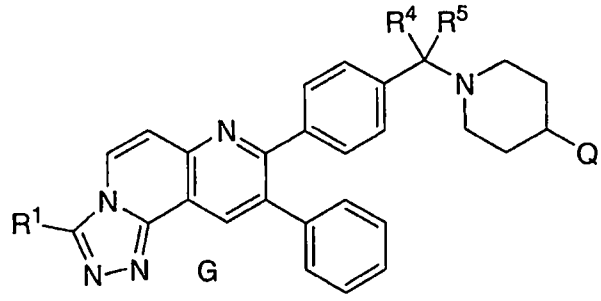
wherein:

$R^1$ is selected from: H, $NH_2$, OH and $(C_1\text{-}C_6)$alkyl;

$R^4$ and $R^5$ are independently: H and $(C_1\text{-}C_6)$alkyl;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In an eighth embodiment the inhibitors of the instant invention are illustrated by the Formula G:



wherein:

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;

Q is selected from: heterocyclyl, which is optionally substituted with one or more substituents selected from $R^{6a}$;

$R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^4$ and $R^5$ are independently: H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, wherein said alkyl is optionally substituted with up to three substituents selected from: OH and halo; and wherein $R^4$ and $R^5$ can be taken together to form a $(C_3\text{-}C_7)$cycloalkyl, wherein said cycloalkyl is optionally substituted with up to three substituents selected from $R^6$;

$R^6$ is: $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$;

$R^7$ and $R^8$ are independently selected from: H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O

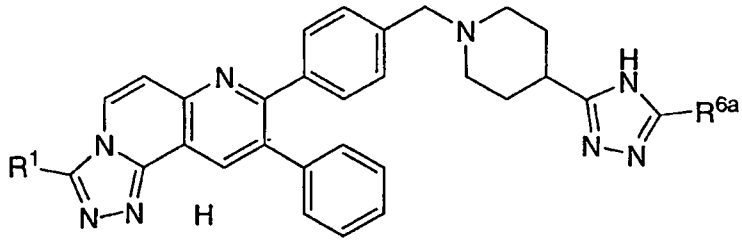
and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

$R^b$ is independently: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)_a O_b(C_1\text{-}C_6)$alkyl, or $S(O)_m R^a$;

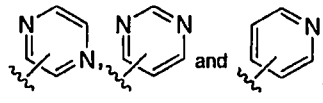
or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a nineth embodiment the inhibitors of the instant invention are illustrated by the Formula H:



wherein:

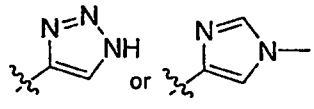
$R^1$ is heterocyclyl, said heterocyclyl optionally substituted with from one to three substituents selected from: $(C_1\text{-}C_6)$alkyl, OH, halo, and $NH_2$;

$R^{6a}$ is selected from:  ; and

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In a tenth embodiment the inhibitors of the instant invention are illustrated by the Formula H:

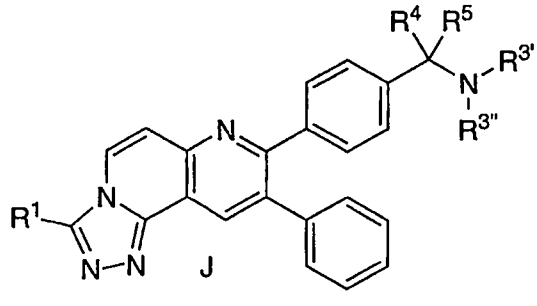
wherein:

$R^1$ is selected from:  ;

and all other substituents and variables are as defined in the nineth embodiment;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

In an eleventh embodiment the inhibitors of the instant invention are illustrated by the Formula J:



wherein:

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;

$R^1$ is selected from: $CF^3$, H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one to six substituents selected from $R^6$;

$R^{3'}$ and $R^{3''}$ are independently selected from: $CF^3$, H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one to five substituents selected from $R^6$; or $R^{3'}$ and $R^{3''}$ can be taken together with the nitrogen to which they are attached to form a piperidine or pyrrolidine which may be optionally substituted with one to five substituents selected from $R^6$;

$R^4$ and $R^5$ are independently: H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, wherein said alkyl is optionally substituted with up to three substituents selected from: OH and halo; and wherein $R^4$ and $R^5$ can be taken together to form a $(C_3\text{-}C_7)$cycloalkyl, wherein said cycloalkyl is optionally substituted with up to three substituents selected from $R^6$;

$R^6$ is: $CF^3$, $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one to five substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $CF^3$, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $(C=O)_aNR^b{}_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$;

$R^7$ and $R^8$ are independently selected from: $CF^3$, H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one to five substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one to six substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $NR^b{}_2$, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

$R^b$ is independently: H, $(C_1\text{-}C_6)$alkyl, $NH_2$, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)_aO_b(C_1\text{-}C_6)$alkyl, or $S(O)_mR^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

Specific compounds of the instant invention include:

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-amine (**1-4**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol (**1-5**);

9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**1-6**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-thiol (**1-7**);

3-methyl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4 ]triazolo[3,4-f]-1,6-naphthyridine (**2-2**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-3**);

3-(chloromethyl)-9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-4**);

3-[(4-methylpiperazin-1-yl)methyl]-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-5**); and

2-({[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}amino)ethanol (**2-6**);

or a pharmaceutically acceptable salt or stereoisomer thereof.

Examples of the compounds of the instant invention include TFA salts of the following compounds:

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-amine (**1-4**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol (**1-5**);

9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**1-6**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-thiol (**1-7**);

3-methyl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4 ]triazolo[3,4-f]-1,6-naphthyridine (**2-2**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-3**);

3-(chloromethyl)-9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-4**);

3-[(4-methylpiperazin-1-yl)methyl]-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-5**);

2-({[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}amino)ethanol (**2-6**);

3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-9**);

3-imidazo[2,1-b][1,3] thiazol-6-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-10**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-[1,2,4]triazolo [1,5-a]pyrimidin-2-yl[1,2,4] triazolo[3,4-f]-1,6-naphthyridine (**9-11**);

3-imidazo[1,2-a]pyridin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-12**);

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-3**);

5-[({4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amino)methyl]pyridin-2-ol (**13-8**);

$N^1$,$N^1$,2,2-tetramethyl-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propane-1,3-diamine (**13-9**);

$N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(4-hydroxyphenyl)-beta-alaninamide (**14-6**);

1-[4-(9-phenyl-3-pyridin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-13**);

4-[3-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-41**);

1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1-benzothien-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-42**);

1-{4-[3-(1-isopropyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-43**);

1-{4-[9-phenyl-3-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-44**);

1-[4-(3-cyclopropyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-48**);

1-{4-[9-phenyl-3-(trifluoromethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-49**);

1-{4-[3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-50**);

1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-51**);

4-[3-(1H-indol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylaminen (**16-52**);
1-{4-[3-(1-methyl-1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-53**);
1-{4-[3-(3-methyl-2H-3lambda~5~-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-54**);
4-[3-(6-chloroimidazo[1,2-a]pyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-55**);
1-{4-[3-(1H-benzimidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-56**);
4-[3-(5-cyclopropyl-4H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-57**);
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1H-indazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-58**);
4-[9-phenyl-3-(3-phenyl-1H-pyrazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-59**);
1-(4-{9-phenyl-3-[3-(trifluoromethyl)-1H-pyrazol-5-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-60**);
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-61**);
1-{4-[3-(1-benzyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-62**);
1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-63**);
4-[9-phenyl-3-(1-phenyl-1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-64**);
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-2-benzothien-1-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-65**);
1-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethane-1,2-diol (**16-68**);
4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}imidazolidin-2-one (**16-69**);
(2R)-2-amino-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol (**16-70**);
(2R)-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2-(methylamino)ethanol (**16-71**);
1-[4-(3-ethyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**17-6**);
1-[4-(9-phenyl-3-propyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**17-7**);
1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropanamine (**33-5**);

1-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl] phenyl}cyclo propanamine (**33-6**);

1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-*a*] pyrimidin-2-yl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] cyclopropanamine (**33-7**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-4-yl-2-furamide (**39-2**);

(3-methyl-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino]cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-43**);

3-methyl-9-phenyl-8-(4-{1-[(quinolin-3-yl carbonyl) amino] cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-44**);

3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino] cyclopropyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-46**);

1-[4-(9-ethyl-2-phenyl[1,2,4]triazolo[4',3':1,6]pyrido[2,3-*b*]pyrazin-3-yl)phenyl]cyclopropanamine (**42-6**); and

1-[4-(9-ethyl-3-phenyl[1,2,4]triazolo[4',3':1,6]pyrido[2,3-*b*]pyrazin-2-yl)phenyl]cyclopropanamine (**42-7**);

or a stereoisomer thereof.

Examples of the compounds of the instant invention include formic acid salts of the following compounds:

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-amine (**1-4**); and

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol (**1-5**);

or a stereoisomer thereof.

Specific compounds of the instant invention include:

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-amine (**1-4**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol (**1-5**);

9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**1-6**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-thiol (**1-7**);

3-methyl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4 ]triazolo[3,4-f]-1,6-naphthyridine (**2-2**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-3**);

3-(chloromethyl)-9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-4**);

3-[(4-methylpiperazin-1-yl)methyl]-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-5**);

2-({[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}amino)ethanol (**2-6**);

8-(4-Aminomethyl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (**3-8**);

1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**4-3**);

4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine (**5-3**);

8-[4-(Aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-2**);

1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**7-4**); and

9-Phenyl-8-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,2,4] triazolo[3,4-*f*][1,6]naphthyridine (**8-10**)

or a pharmaceutically acceptable salt or stereoisomer thereof.

Examples of the compounds of the instant invention include HCl salts of the following compounds:

8-(4-Aminomethyl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (**3-8**);

1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**4-3**);

4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine (**5-3**);

8-[4-(Aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-2**); and

1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**7-4**);

3-(1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-5**);

tert-butyl [9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-yl]methylcarbamate (**9-6**);

[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**9-7**);

5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**9-8**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,4-triazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-13**);

3-(1H-benzimidazol-6-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-14**);

3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-15**);

3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-16**);

5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine (**9-17**);

9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-18**);

3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-19**);

3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine (**9-20**);

4-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol (**9-21**);

3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol (**9-22**);

2-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol (**9-23**);

1-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide (**9-24**);

1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]piperidine-4-carboxamide (**9-25**);

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-3**);

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-4**);

N-[2-(4-methyl-1H-imidazol-2-yl)ethyl]-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amine (**13-5**);

$N^1$-(2-hydroxyphenyl)-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-beta-alaninamide (**13-6**);

1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide (**13-7**);

3-hydroxy-2,2-dimethyl-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-10**);

2-fluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-11**);

2,2-difluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-12**);

2,3-dihydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-13**);

4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine (**13-14**);

4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine (**13-15**);

3-hydroxy-2,2-dimethyl-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}propan-1-amine (**13-16**);

3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-17**);

3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-18**);

3-hydroxy-2,2-dimethyl-N-{4-[9-phenyl-3-(1H-1,2,3-triazol-4-yl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propan-1-amine (**13-19**);

N-{4-[3-(ammoniomethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-3-hydroxy-2,2-dimethylpropan-1-amine (**13-21**);

$N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(2-hydroxyphenyl)-beta-alaninamide (**14-4**);

(8-{4-[(cyclohexylamino)methyl]phenyl}-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl)methanol (**14-5**);

[9-phenyl-8-(4-{[4-(5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**14-7**);

1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide (**14-8**);

1-{4-[3-(1-oxidopyridin-3-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] phenyl}methanamine (**16-4**);

1-[4-(3,9-diphenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-5**);

1-{4-[3-(4-fluorophenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-6**);

4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}benzonitrile (**16-7**);

4-(9-phenyl-3-pyrimidin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine (**16-8**);

1-{4-[3-(1-oxidopyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-9**);

5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}yridine-2-ol (**16-10**);

1-[4-(9-phenyl-3-pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-11**);

4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine (**16-12**);

1-[4-(9-phenyl-3-pyrazin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-14**);

1-{4-[9-phenyl-3-(1H-1,2,4-triazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**16-15**);

1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-16**);

1-{4-[9-phenyl-3-(1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine

(**16-17**);
1-{4-[3-(3-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-18**);
1-{4-[3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-19**);
1-{4-[3-(1-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-20**);
1-{4-[9-phenyl-3-(1,2,5-thiadiazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-21**);
1-{4-[9-phenyl-3-(1,2,3-thiadiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-22**);
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-23**);
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanamine (**16-24**);
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol (**16-25**);
1-{4-[9-phenyl-3-(2,2,2-trifluoroethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-26**);
1-{4-[9-phenyl-3-(1H-tetraazol-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-27**);
8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine-3-carboxamide (**16-28**);
1-{4-[3-(1H-imidazol-1-ylmethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**16-29**);
1-(4-{3-[(methylsulfonyl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-30**);
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}acetonitrile (**16-31**);
2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol (**16-32**);
N-({8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methyl)acetamide (**16-33**);
1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-36**);
1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-38**);
1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-40**);
1-(4-{9-phenyl-3-[(2R)-pyrrolidin-2-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-44**);
1-(4-{9-phenyl-3-[(2S)-pyrrolidin-2-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-45**);

4-[3-(1-aminoethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-46**);
1-{4-[3-(1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-47**);
1-{4-[9-phenyl-3-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-66**);
2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}propan-2-amine (**16-67**);
1-{4-[3-(5-ethylisoxazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-72**);
5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2,4-dihydro-3H-1,2,4-triazol-3-one (**16-73**);
6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-4,5-dihydropyridazin-3(2H)-one (**16-74**);
6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}pyridazin-3(2H)-one (**16-75**);
N-(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)acetamide (**16-76**);
1-{4-[3-(4-phenoxyphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-77**);
1-{4-[3-(1H-benzimidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-78**);
(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)methanol (**16-79**);
4-[3-(4-cyclohexylphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-80**);
4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-1,3-dihydro-2H-imidazol-2-one (**16-81**);
1-{4-[3-(4-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**16-82**);
4-[9-phenyl-3-(1-propyl-1H-imidazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-83**);
1-{4-[3-(1-isopropyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-84**);
1-{4-[3-(1-butyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-85**);
1-[4-(3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-86**);
1-(6-methoxypyridin-3-yl)-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]methanamine (**17-4**);

N-[(2-methoxypyrimidin-5-yl)methyl]-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amine (**17-5**);

9-phenyl-3-(1H-1,2,3-triazol-4-yl)-8-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**21-4**);

1-{4-[9-phenyl-3-(3H-1lambda$^4$,3-thiazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-4**);

1-{4-[9-phenyl-3-(1H-pyrazol-3-yl)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-5**);

1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-6**);

1-{4-[3-(azetidin-1-ylmethyl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**26-3**);

1-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)piperidine-4-carboxamide (**26-4**);

1-{4-[3-(morpholin-4-ylmethyl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**26-5**);

2-[({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)amino]ethanol (**26-6**);

1-(4-{3-[(4-methyl piperazin-1-yl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**26-7**);

4-[9-phenyl-3-(piperazin-1-ylmethyl)[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**26-8**);

N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N-methylamine (**26-9**);

N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N,N-dimethylamine (**26-10**);

3-methyl-9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl] methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**31-1**);

1-{4-[9-phenyl-3-(5,6,7,8-tetrahydro imidazo[1,2-a]pyridin-2-yl)[1,2,4] triazolo [3,4-f]-1,6-naphthyridin -8-yl] phenyl}cyclo propanamine (**33-8**);

1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]cyclopropanamine (**33-9**);

1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}cyclopropanamine (**33-10**);

(1R)-1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl ]ethanamine (**34-5**);

(1*R*)-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**34-6**);

(1*R*)-1-{4-[9-Phenyl-3-(5-pyridin-2-yl-1*H*-pyrazol-3-yl)[1,2,4]triazolo[3,4-*f*]-1,6- naphthyridin-8-yl]phenyl}ethanamine (**35-1**);

(1R)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine (**35-2**);

(1R)-1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine (**35-3**);

(1R)-1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**35-4**);

(1R)-1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**35-5**);

(1R)-1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**35-6**);

(1*R*)-1-[4-(9-Phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-1-amine (**36-1**);

2-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine (**37-4**)

2-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine (**38-1**);

3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl) pyridine (**39-1**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-2-furamide (**39-3**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-1*H*-pyrrole-3-carboxamide (**39-4**);

4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)morpholine (**39-7**);

2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethanamine (**39-8**);

4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine (**39-9**);

2,4-dihydroxy-6-(2-{[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyrimidine (**39-10**);

2-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine (**39-11**);

3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine (**39-12**);

3-methyl-9-phenyl-8-[4-({[(pyridin-3-ylamino) carbonyl]amino}methyl)phenyl][1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-14**);

3-methyl-9-phenyl-8-(4-{[(pyridin-3-ylcarbonyl) amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-20**);

3-methyl-9-phenyl-8-(4-{[(quinolin-3-ylcarbonyl) amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-26**);

8-(4-{[(1*H*-benzimidazol-1-ylacetyl)amino]methyl} phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-29**);

8-(4-{[(1*H*-benzimidazol-2-ylacetyl)amino]methyl} phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-30**);

3-methyl-8-[4-({[(6-morpholin-4-ylpyridin-3-yl)carbonyl]amino}methyl)phenyl]-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine (**39-34**);

3-methyl-9-phenyl-8-(4-{[(3-pyridin-3-yl propanoyl)amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-37**);

3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{[(pyridin-3-ylacetyl)amino]methyl}phenyl)[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine (**39-38**);

9-phenyl-3-pyrazolo[1,5-*a*]pyrimidin-3-yl-8-(4-{[(pyridin-3-ylacetyl)amino]methyl}phenyl)[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine (**39-39**);

*N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}-2-pyridin-3-ylacetamide (**39-47**); and

*N*-((1*R*)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}ethyl)-2-pyridin-3-ylacetamide (**39-49**);

or a stereoisomer thereof.

Further specific compounds of the instant invention include:

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-amine (**1-4**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol (**1-5**);

9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**1-6**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-thiol (**1-7**);

3-methyl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4 ]triazolo[3,4-f]-1,6-naphthyridine (**2-2**);

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-3**);

3-(chloromethyl)-9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-4**);

3-[(4-methylpiperazin-1-yl)methyl]-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-5**);

2-({[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}amino)ethanol (**2-6**);

8-(4-Aminomethyl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (**3-8**);

1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**4-3**);

4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine (**5-3**);
8-[4-(Aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-2**);
1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**7-4**);
9-Phenyl-8-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,2,4] triazolo[3,4-*f*][1,6]naphthyridine (**8-10**);
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-4**);
3-(1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-5**);
tert-butyl [9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-yl]methylcarbamate (**9-6**);
[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**9-7**);
5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]-2,4-dihydro-3H-1,2,4-triazol-3-one (**9-8**);
3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-9**);
3-imidazo[2,1-b][1,3] thiazol-6-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-10**);
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-[1,2,4]triazolo [1,5-a]pyrimidin-2-yl[1,2,4] triazolo[3,4-f]-1,6-naphthyridine (**9-11**);
3-imidazo[1,2-a]pyridin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-12**);
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,4-triazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-13**);
3-(1H-benzimidazol-6-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-14**);
3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-15**);
3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-16**);
5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine (**9-17**);
9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-18**);
3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-19**);

3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine (**9-20**);

4-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol (**9-21**);

3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol (**9-22**);

2-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol (**9-23**);

1-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide (**9-24**);

1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]piperidine-4-carboxamide (**9-25**);

9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**10-4**);

9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**11-4**);

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**12-1**);

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-3**);

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-4**);

N-[2-(4-methyl-1H-imidazol-2-yl)ethyl]-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzyl}amine (**13-5**);

$N^1$-(2-hydroxyphenyl)-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-beta-alaninamide (**13-6**);

1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide (**13-7**);

5-[({4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amino)methyl]pyridin-2-ol (**13-8**);

$N^1$,$N^1$,2,2-tetramethyl-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propane-1,3-diamine (**13-9**);

3-hydroxy-2,2-dimethyl-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-10**);

2-fluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-11**);

2,2-difluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-12**);

2,3-dihydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-13**);

4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine (**13-14**);

4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine (**13-15**);

3-hydroxy-2,2-dimethyl-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}propan-1-amine (**13-16**);

3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-17**);

3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine (**13-18**);

3-hydroxy-2,2-dimethyl-N-{4-[9-phenyl-3-(1H-1,2,3-triazol-4-yl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propan-1-amine (**13-19**);

tert-butyl {[8-(4-{[(3-hydroxy-2,2-dimethylpropyl)amino]methyl}phenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}carbamate (**13-20**);

N-{4-[3-(ammoniomethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-3-hydroxy-2,2-dimethylpropan-1-amine (**13-21**);

[9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**14-3**);

$N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(2-hydroxyphenyl)-beta-alaninamide (**14-4**);

(8-{4-[(cyclohexylamino)methyl]phenyl}-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl)methanol (**14-5**);

$N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(4-hydroxyphenyl)-beta-alaninamide (**14-6**);

[9-phenyl-8-(4-{[4-(5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**14-7**);

1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide (**14-8**);

{8-[4-(1-aminocyclopropyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol (**15-2**);

1-[4-(9-phenyl-3-pyridin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-3**);

1-{4-[3-(1-oxidopyridin-3-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] phenyl}methanamine (**16-4**);

1-[4-(3,9-diphenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-5**);

1-{4-[3-(4-fluorophenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-6**);

4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}benzonitrile (**16-7**);
4-(9-phenyl-3-pyrimidin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine (**16-8**);
1-{4-[3-(1-oxidopyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-9**);
5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}yridine-2-ol (**16-10**);
1-[4-(9-phenyl-3-pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-11**);
4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine (**16-12**);
1-[4-(9-phenyl-3-pyridin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-13**);
1-[4-(9-phenyl-3-pyrazin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-14**);
1-{4-[9-phenyl-3-(1H-1,2,4-triazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**16-15**);
1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-16**);
1-{4-[9-phenyl-3-(1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-17**);
1-{4-[3-(3-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-18**);
1-{4-[3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-19**);
1-{4-[3-(1-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-20**);
1-{4-[9-phenyl-3-(1,2,5-thiadiazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-21**);
1-{4-[9-phenyl-3-(1,2,3-thiadiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-22**);
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-23**);
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanamine (**16-24**);
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol (**16-25**)
1-{4-[9-phenyl-3-(2,2,2-trifluoroethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-26**);
1-{4-[9-phenyl-3-(1H-tetraazol-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-27**);
8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine-3-carboxamide (**16-28**);
1-{4-[3-(1H-imidazol-1-ylmethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**16-29**);
1-(4-{3-[(methylsulfonyl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-30**);

{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}acetonitrile (**16-31**);
2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol (**16-32**);
N-({8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methyl)acetamide (**16-33**);
4-[3-(2-methylimidazo[1,2-a]pyridin-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-34**);
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-35**);
1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-36**);
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-37**);
1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-38**);
1-{4-[3-(1-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-39**);
1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-40**);
4-[3-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-41**);
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1-benzothien-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-42**);
1-{4-[3-(1-isopropyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-43**);
1-{4-[9-phenyl-3-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-44**);
1-(4-{9-phenyl-3-[(2S)-pyrrolidin-2-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-45**);
4-[3-(1-aminoethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-46**);
1-{4-[3-(1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-47**);
1-[4-(3-cyclopropyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-48**);
1-{4-[9-phenyl-3-(trifluoromethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-49**);
1-{4-[3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-50**);
1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-51**);

4-[3-(1H-indol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylaminen (**16-52**);
1-{4-[3-(1-methyl-1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-53**);
1-{4-[3-(3-methyl-2H-3lambda$^5$-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-54**);
4-[3-(6-chloroimidazo[1,2-a]pyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-55**);
1-{4-[3-(1H-benzimidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-56**);
4-[3-(5-cyclopropyl-4H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-57**);
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1H-indazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-58**);
4-[9-phenyl-3-(3-phenyl-1H-pyrazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-59**);
1-(4-{9-phenyl-3-[3-(trifluoromethyl)-1H-pyrazol-5-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**16-60**);
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-61**);
1-{4-[3-(1-benzyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-62**);
1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-63**);
4-[9-phenyl-3-(1-phenyl-1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-64**);
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-2-benzothien-1-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-65**);
1-{4-[9-phenyl-3-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-66**);
2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}propan-2-amine (**16-67**);
1-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethane-1,2-diol (**16-68**);
4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}imidazolidin-2-one (**16-69**);
(2R)-2-amino-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol (**16-70**);

(2R)-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2-(methylamino)ethanol (**16-71**);

1-{4-[3-(5-ethylisoxazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-72**);

5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2,4-dihydro-3H-1,2,4-triazol-3-one (**16-73**);

6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-4,5-dihydropyridazin-3(2H)-one (**16-74**);

6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}pyridazin-3(2H)-one (**16-75**);

N-(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)acetamide (**16-76**);

1-{4-[3-(4-phenoxyphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-77**);

1-{4-[3-(1H-benzimidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-78**);

(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)methanol (**16-79**);

4-[3-(4-cyclohexylphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-80**);

4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-1,3-dihydro-2H-imidazol-2-one (**16-81**);

1-{4-[3-(4-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-82**);

4-[9-phenyl-3-(1-propyl-1H-imidazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**16-83**);

1-{4-[3-(1-isopropyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-84**);

1-{4-[3-(1-butyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**16-85**);

1-[4-(3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-86**);

5-({[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amino}methyl)pyridin-2-ol (**17-3**);

1-(6-methoxypyridin-3-yl)-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]methanamine (**17-4**);

N-[(2-methoxypyrimidin-5-yl)methyl]-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amine (**17-5**);

1-[4-(3-ethyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**17-6**);

1-[4-(9-phenyl-3-propyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**17-7**);
N-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]acetamide (**18-1**);
4-({[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amino}methyl)phenol (**19-1**);
1-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl] methyl}phenyl)[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-yl]methanamine (**20-1**);
9-phenyl-3-(1H-1,2,3-triazol-4-yl)-8-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**21-4**);
1-{4-[3-(1H-Imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-3**);
1-{4-[9-phenyl-3-(3H-1lambda$^4$,3-thiazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-4**);
1-{4-[9-phenyl-3-(1H-pyrazol-3-yl)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-5**);
1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-6**);
4-[9-Phenyl-3-(pyrrolidin-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**26-2**);
1-{4-[3-(azetidin-1-ylmethyl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**26-3**);
1-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)piperidine-4-carboxamide (**26-4**);
1-{4-[3-(morpholin-4-ylmethyl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine (**26-5**);
2-[({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)amino]ethanol (**26-6**);
1-(4-{3-[(4-methyl piperazin-1-yl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine (**26-7**);
4-[9-phenyl-3-(piperazin-1-ylmethyl)[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**26-8**);
N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N-methylamine (**26-9**);
N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N,N-dimethylamine (**26-10**);
[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]methanol (**28-1**);
{4-[3-(1-Methyl-1*H*-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}methanol (**28-2**);
1-[4-(9-Phenyl-3-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanol (**29-2**);
9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**30-1**);

3-methyl-9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl] methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**31-1**);

9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-3-ol (**32-1**);

1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropanamine (**33-5**);

1-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl] phenyl}cyclo propanamine (**33-6**);

1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-*a*] pyrimidin-2-yl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] cyclopropanamine (**33-7**);

1-{4-[9-phenyl-3-(5,6,7,8-tetrahydro imidazo[1,2-a]pyridin-2-yl)[1,2,4] triazolo [3,4-f]-1,6-naphthyridin -8-yl] phenyl}cyclo propanamine (**33-8**);

1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]cyclopropanamine (**33-9**);

1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}cyclopropanamine (**33-10**);

(1R)-1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl ]ethanamine (**34-5**);

(1*R*)-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**34-6**);

(1*R*)-1-{4-[9-Phenyl-3-(5-pyridin-2-yl-1*H*-pyrazol-3-yl)[1,2,4]triazolo[3,4-*f*]-1,6- naphthyridin-8-yl]phenyl}ethanamine (**35-1**);

(1R)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine (**35-2**);

(1R)-1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine (**35-3**);

(1R)-1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**35-4**);

(1R)-1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**35-5**);

(1R)-1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine (**35-6**);

(1*R*)-1-[4-(9-Phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-1-amine (**36-1**);

2-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine (**37-4**)

2-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine (**38-1**);

3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl) pyridine (**39-1**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-4-yl-2-furamide (**39-2**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-2-furamide (**39-3**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-1*H*-pyrrole-3-carboxamide (**39-4**);

2-hydroxy-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-5**);

*tert*-butyl (2-{[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]amino}-2-oxoethyl)carbamate (**39-6**);

4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)morpholine (**39-7**);

2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethanamine (**39-8**);

4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine (**39-9**);

2,4-dihydroxy-6-(2-{[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyrimidine (**39-10**);

2-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine (**39-11**);

3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine (**39-12**);

*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-pyrazin-2-ylacetamide (**39-13**);

3-methyl-9-phenyl-8-[4-({[(pyridin-3-ylamino) carbonyl]amino}methyl)phenyl][1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-14**);

2-(2-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-15**);

2-(3-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-16**);

2-(4-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-17**);

2-(3,4-dihydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-18**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl] -2-phenylacetamide (**39-19**);

3-methyl-9-phenyl-8-(4-{[(pyridin-3-ylcarbonyl) amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-20**);

2-hydroxy-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]benzamide (**39-21**);

2-(4-hydroxyphenyl)-2-methyl-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]propanamide (**39-22**);

methyl 4-{[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-4-oxobutanoate (**39-23**);

2-hydroxy-*N*-(2-{[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]amino}-2-oxoethyl)benzamide (**39-24**);

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl] -2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetamide (**39-25**);

3-methyl-9-phenyl-8-(4-{[(quinolin-3-ylcarbonyl) amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-26**);

*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide (**39-27**);

*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetamide (**39-28**);

8-(4-{[(1*H*-benzimidazol-1-ylacetyl)amino]methyl} phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-29**);

8-(4-{[(1*H*-benzimidazol-2-ylacetyl)amino]methyl} phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-30**);

2-(4-methyl-1,2,5-oxadiazol-3-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-31**);

2-(1*H*-indazol-1-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide (**39-32**);

2-(5,6-dimethyl-4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide (**39-33**);

3-methyl-8-[4-({[(6-morpholin-4-ylpyridin-3-yl)carbonyl]amino}methyl)phenyl]-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine (**39-34**);

2-(6-chloropyridin-3-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide (**39-35**);

3-cyano-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]propanamide (**39-36**);

3-methyl-9-phenyl-8-(4-{[(3-pyridin-3-yl propanoyl)amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-37**);

3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{[(pyridin-3-ylacetyl)amino]methyl}phenyl)[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine (**39-38**);

9-phenyl-3-pyrazolo[1,5-*a*]pyrimidin-3-yl-8-(4-{[(pyridin-3-ylacetyl)amino]methyl}phenyl)[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine (**39-39**);

*N*-(3-hydroxy-2,2-dimethylpropyl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl ) benzyl]acetamide (**39-40**);

*N*-(3-hydroxy-2,2-dimethylpropyl)-*N*-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl ] benzyl}-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide (**39-41**);

*tert*-butyl {2-[[4-(3-{[(*tert*-butoxycarbonyl) amino]methyl}-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl](3-hydroxy-2,2-dimethylpropyl)amino]-2-oxoethyl}carbamate (**39-42**);

3-methyl-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino]cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-43**);

3-methyl-9-phenyl-8-(4-{1-[(quinolin-3-yl carbonyl) amino] cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-44**);

*N*-{1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropyl}-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide (**39-45**);

3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino] cyclopropyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine (**39-46**);

*N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}-2-pyridin-3-ylacetamide (**39-47**);

*N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}acetamide (**39-48**);

*N*-((1*R*)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}ethyl)-2-pyridin-3-ylacetamide (**39-49**);

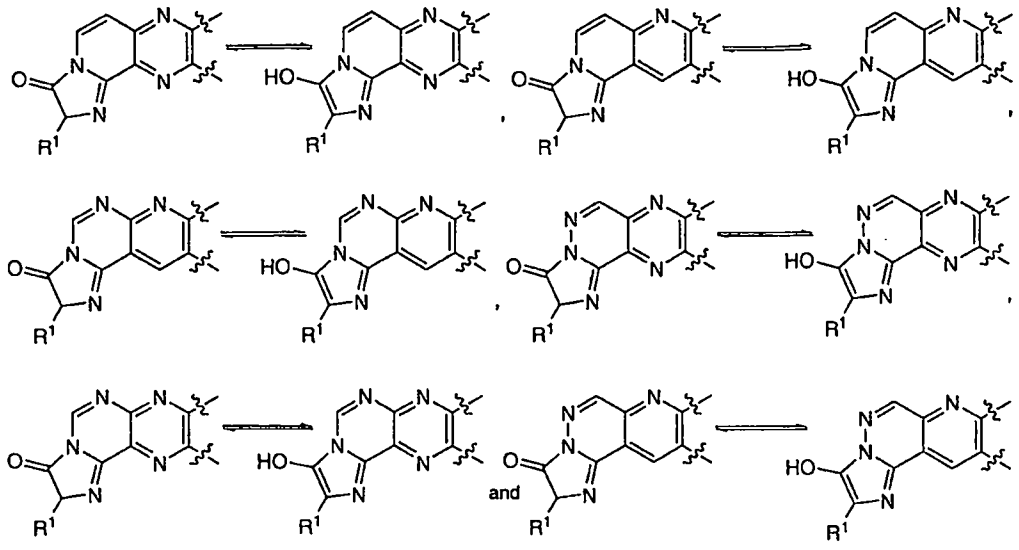
*N*-{1-methyl-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl}acetamide (**39-50**); and

*N*-{1-methyl-1-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl} acetamide (**39-51**);

or a pharmaceutically acceptable salt or stereoisomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention.

In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted. For example the following is within the scope of the instant invention:



Tetrazoles exist as a mixture of 1H/2H tautomers. The tautomeric forms of the tetrazol moiety are also within the scope of the instant invention.

When any variable (e.g. $R^2$, etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is bicyclic, it is intended that the bond be attached to any of the suitable atoms on either ring of the bicyclic moiety.

It is understood that one or more silicon (Si) atoms can be incorporated into the compounds of the instant invention in place of one or more carbon atoms by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art from readily available starting materials. Carbon and silicon differ in their covalent radius leading to differences in bond distance and the steric arrangement when comparing analogous C-element and Si-element bonds. These differences lead to subtle changes in the size and shape of silicon-containing compounds when compared to carbon. One of ordinary skill in the art would understand that size and shape differences can lead to subtle or dramatic changes in potency, solubility, lack of off target activity, packaging properties, and so on. (Diass, J. O. *et al.* Organometallics (2006) 5:1188-1198; Showell, G.A. et al. Bioorganic & Medicinal Chemistry Letters (2006) 16:2555-2558).

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one

substituent" and in such cases the preferred embodiment will have from zero to four substituents, and the more preferred embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, $C_1$-$C_{10}$, as in "($C_1$-$C_{10}$)alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrange-ment. For example, "($C_1$-$C_{10}$)alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "($C_2$-$C_{10}$)alkenyl" means an alkenyl radical having from 2 to 10 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "($C_2$-$C_{10}$)alkynyl" means an alkynyl radical having from 2 to 10 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as ($C_0$-$C_6$)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -$CH_2$Ph, -$CH_2CH_2$Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydro-naphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

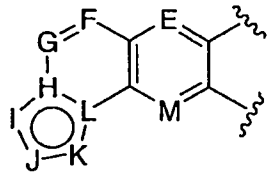
The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl,

isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. Such heteraoaryl moieties for substituent Q include but are not limited to: 2-benzimidazolyl, 2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 1-isoquinolinyl, 3-isoquinolinyl and 4-isoquinolinyl.

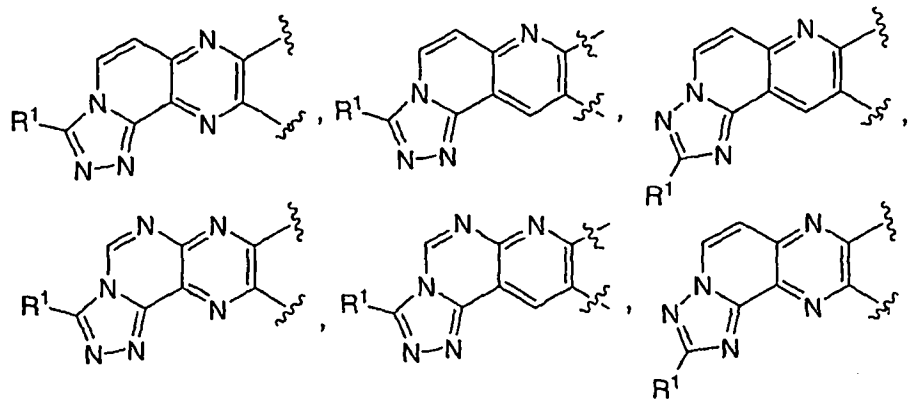
The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzoimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

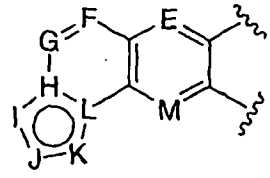
In an embodiment of Formula A, B, C or D, the moiety illustrated by the formula:



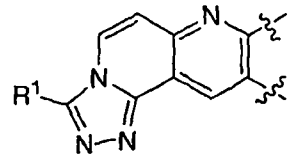

includes the following structures, which are meant to be merely illustrative and not limiting:



In another embodiment of Formula A, B, C or D, the moiety illustrated by the formula:

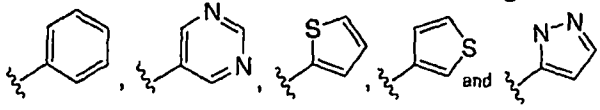


is:



In an embodiment, ring Z is selected from: phenyl and heterocyclyl.

In another embodiment, ring Z is selected from:



In yet another embodiment, ring Z is phenyl.

In an embodiment, p is independently 0, 1, 2 or 3.

In a further embodiment, p is independently 0, 1 or 2.

In another embodiment, p is independently 1.

In an embodiment, r is 0, 1, 2 or 3.

In a further embodiment, r is 0, 1 or 2.

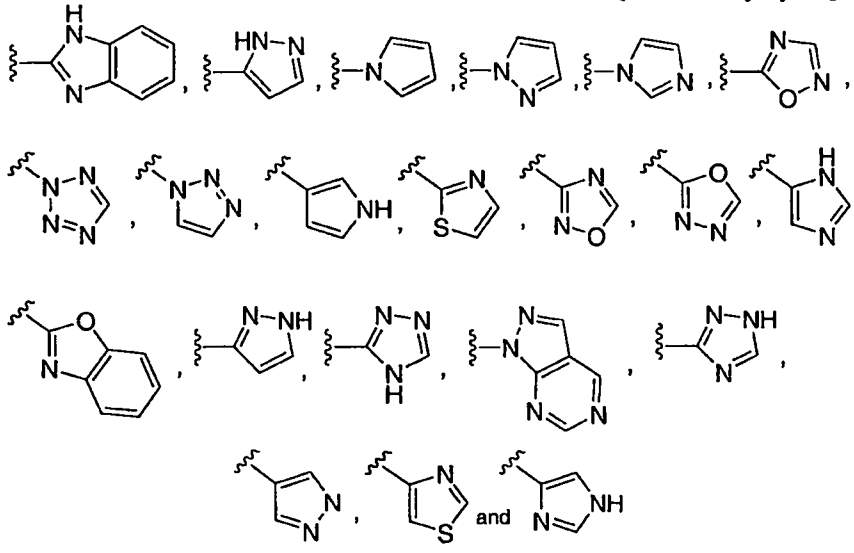
In another embodiment, r is 1.

In an embodiment, Q is selected from: benzoimidazolyl, benzoimidazolonyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl,

oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof, optionally substituted with one to three substituents selected from $R^{6a}$. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

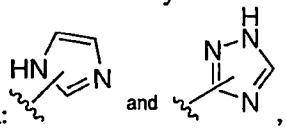
In a further embodiment, Q is selected from: 2-azepinone, benzimidazolyl, benzimidazolonyl, 2-diazapinone, imidazolyl, 2-imidazolidinone, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinone, 2-pyrimidinone, 2-pyrollidinone, quinolinyl, tetrazolyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl, optionally substituted with one to three substituents selected from $R^{6a}$. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

In still a further embodiment, when Q is heterocyclyl, Q is selected from:



, which are optionally substituted with one to threee substituents selected from $R^{6a}$.

In yet a further embodiment, when Q is heterocyclyl, Q is selected from:



, which is optionally substituted with one substituent selected from $R^{6a}$.

In an embodiment, $R^1$ is selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_2NR^7R^8$, SH, $S(O)_2\text{-}(C_1\text{-}C_{10})$alkyl and

$(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with $R^{6a}$.

In another embodiment, $R^1$ is selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $CO_2H$, halo, OH, CN, $(C_1\text{-}C_6)$alkoxy, $S(O)_2NR^7R^8$, SH, $S(O)_2\text{-}(C_1\text{-}C_{10})$alkyl, $O(C=O)(C_1\text{-}C_6)$alkyl and $N(R^b)_2$, said alkyl is optionally substituted with $R^{6a}$.

In another embodiment, $R^1$ is selected from: oxo, $NH_2$, OH, SH, $O_a(C_1\text{-}C_6)$alkyl, said alkyl is optionally substituted with $R^{6a}$.

In an embodiment, $R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_2NR^7R^8$, SH, $S(O)_2\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with $R^{6a}$.

In another embodiment, $R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $CO_2H$, halo, OH, CN, $(C_1\text{-}C_6)$alkoxy, $S(O)_2NR^7R^8$, SH, $S(O)_2\text{-}(C_1\text{-}C_{10})$alkyl, $O(C=O)(C_1\text{-}C_6)$alkyl and $N(R^b)_2$, said alkyl is optionally substituted with $R^{6a}$.

In another embodiment, $R^1$ is selected from: H, oxo, $NH_2$, OH, SH, $O_a(C_1\text{-}C_6)$alkyl, said alkyl is optionally substituted with $R^{6a}$.

In an embodiment, $R^2$ is selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_2NR^7R^8$, $S(O)_2\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O(C=O)(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$.

In another embodiment, $R^2$ is selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $CO_2H$, halo, OH, CN, $(C_1\text{-}C_6)$alkoxy, $O(C=O)(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_{10})$alkenyl and $N(R^b)_2$, said alkyl is optionally substituted with $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O(C=O)(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$.

In an embodiment, $R^3$ is selected from: H, oxo, $O_b(C_1\text{-}C_{10})$alkyl, $O_b$-aryl, $O_b(C_2\text{-}C_{10})$alkenyl, $O_b(C_2\text{-}C_{10})$alkynyl, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$.

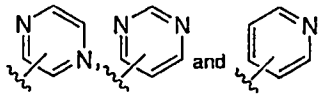
In another embodiment, $R^3$ is selected from: $(C_1\text{-}C_{10})$alkyl, aryl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, halo, $NR^7R^8$, CN, $(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$.

In another embodiment, $R^3$ is selected from: $(C_1\text{-}C_{10})$alkyl, said alkyl is optionally substituted with one to three substituents selected from $NH_2$, OH, oxo and halo.

In another embodiment, $R^4$ and $R^5$ are H.

In an embodiment, when Q is substituted with $R^{6a}$, said $R^{6a}$ is heterocyclyl optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C{=}O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$.

In another embodiment, when Q is substituted with $R^{6a}$, said $R^{6a}$ is selected from:



optionally substituted with 1 to 3 substituents selected from oxo, OH, $N(R^b)_2$, halogen and $O_a(C_1\text{-}C_6)$alkyl.

In an embodiment $R^b$ is independently selected from H and $(C_1\text{-}C_6)$alkyl.

In an embodiment of Formula J, $R^4$ and $R^5$ are independently: H and $CH_3$, or $R^4$ and $R^5$ may be joined to form cyclopropyl.

Included in the instant invention is the free form of compounds of Formula A, as well as the pharmaceutically acceptable salts and stereoisomers thereof. Some of the isolated specific compounds exemplified herein are the protonated salts of amine compounds. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the isolated salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of Formula A. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate, ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic (TFA) and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N$^1$-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

## UTILITY

The compounds of the instant invention are inhibitors of the activity of Akt and are thus useful in the treatment of cancer, in particular cancers associated with irregularities in the activity of Akt and downstream cellular targets of Akt. Such cancers include, but are not limited to, ovarian, pancreatic, breast and prostate cancer, as well as cancers (including glioblastoma) where the tumor suppressor PTEN is mutated (Cheng et al., *Proc. Natl. Acad. Sci.* (1992) 89:9267-9271; Cheng et al., *Proc. Natl. Acad. Sci.* (1996) 93:3636-3641; Bellacosa et al., *Int. J. Cancer* (1995) 64:280-285; Nakatani et al., *J. Biol. Chem.* (1999) 274:21528-21532; Graff, *Expert. Opin. Ther. Targets* (2002) 6(1):103-113; and Yamada and Araki, *J. Cell Science.* (2001) 114:2375-2382; Mischel and Cloughesy, *Brain Pathol.* (2003) 13(1):52-61).

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer. Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma,

adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colorectal, rectal; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

Cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: breast, prostate, colon, colorectal, lung, brain, testicular, stomach, pancrease, skin, small intestine, large intestine, throat, head and neck, oral, bone, liver, bladder, kidney, thyroid and blood.

Cancers that may be treated by the compounds, compositions and methods of the invention include: breast, prostate, colon, ovarian, colorectal and lung.

Cancers that may be treated by the compounds, compositions and methods of the invention include: breast, colon, (colorectal) and lung.

Cancers that may be treated by the compounds, compositions and methods of the invention include: lymphoma and leukemia.

Akt signaling regulates multiple critical steps in angiogenesis. Shiojima and Walsh, *Circ. Res.* (2002) 90:1243-1250. The utility of angiogenesis inhibitors in the treatment of cancer is known in the literature, see J. Rak et al. *Cancer Research*, 55:4575-4580, 1995 and Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966, for example. The role of angiogenesis in cancer has been shown in numerous types of cancer and tissues: breast carcinoma (G. Gasparini and A.L. Harris, *J. Clin. Oncol.*, 1995, 13:765-782; M. Toi et al., *Japan. J. Cancer Res.*, 1994, 85:1045-1049); bladder carcinomas (A.J. Dickinson et al., *Br. J. Urol.*, 1994, 74:762-766); colon carcinomas (L.M. Ellis et al., *Surgery*, 1996, 120(5):871-878); and oral cavity tumors (J.K. Williams et al., *Am. J. Surg.*, 1994, 168:373-380). Other cancers include, advanced tumors, hairy cell leukemia, melanoma, advanced head and neck, metastatic renal cell, non-Hodgkin's lymphoma, metastatic breast, breast adenocarcinoma, advanced melanoma, pancreatic, gastric, glioblastoma, lung, ovarian, non-small cell lung, prostate, small cell lung, renal cell carcinoma, various solid tumors, multiple myeloma, metastatic prostate, malignant glioma, renal cancer, lymphoma, refractory metastatic disease, refractory multiple myeloma, cervical cancer, Kaposi's sarcoma, recurrent anaplastic glioma, and metastatic colon cancer (Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). Thus, the Akt inhibitors disclosed in the instant application are also useful in the treatment of these angiogenesis related cancers.

Tumors which have undergone neovascularization show an increased potential for metastasis. In fact, angiogenesis is essential for tumor growth and metastasis. (S.P. Cunningham, et al., *Can. Research*, 61: 3206-3211 (2001)). The Akt inhibitors disclosed in the present application are therefore also useful to prevent or decrease tumor cell metastasis.

Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention. Ocular neovascular diseases are an example of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye (see WO 00/30651, published 2 June 2000). The undesireable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood vessels by administration of the present compounds would therefore prevent the infiltration of blood vessels and prevent or treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

Further included within the scope of the invention is a method of treating or preventing a non-malignant disease in which angiogenesis is implicated, including but not limited to: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis, psoriasis, obesity and Alzheimer's disease (Dredge et al., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). In another embodiment, a method of treating or preventing a disease in

which angiogenesis is implicated includes: ocular diseases (such as, retinal vascularization, diabetic retinopathy and age-related macular degeneration), atherosclerosis, arthritis and psoriasis.

Further included within the scope of the invention is a method of treating hyperproliferative disorders such as restenosis, inflammation, autoimmune diseases and allergy/asthma.

Further included within the scope of the instant invention is the use of the instant compounds to coat stents and therefore the use of the instant compounds on coated stents for the treatment and/or prevention of restenosis (WO03/032809).

Further included within the scope of the instant invention is the use of the instant compounds for the treatment and/or prevention of osteoarthritis (WO03/035048).

Further included within the scope of the invention is a method of treating hyperinsulinism.

The compounds of the invention are also useful in preparing a medicament that is useful in treating the diseases described above, in particular cancer.

In an embodiment of the invention, the instant compound is a selective inhibitor whose inhibitory efficacy is dependent on the PH domain. In this embodiment, the compound exhibits a decrease in *in vitro* inhibitory activity or no *in vitro* inhibitory activity against truncated Akt proteins lacking the PH domain.

In a further embodiment, the instant compound is selected from the group of a selective inhibitor of Akt1, a selective inhibitor of Akt2 and a selective inhibitor of both Akt1 and Akt2.

In another embodiment, the instant compound is selected from the group of a selective inhibitor of Akt1, a selective inhibitor of Akt2, a selective inhibitor of Akt3 and a selective inhibitor of two of the three Akt isoforms.

In another embodiment, the instant compound is a selective inhibitor of all three Akt isoforms, but is not an inhibitor of one, two or all of such Akt isoforms that have been modified to delete the PH domain, the hinge region or both the PH domain and the hinge region.

The present invention is further directed to a method of inhibiting Akt activity which comprises administering to a mammal in need thereof a pharmaceutically effective amount of the instant compound.

The compounds of this invention may be administered to mammals, including humans, either alone or, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, 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 elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate 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, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, 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, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil 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 a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient 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. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. 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 phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

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, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. 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.

Compounds of Formula A may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated

gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula A are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

The dosage regimen utilizing the compounds of the instant invention can be selected in accordance with a variety of factors including type, species, age, weight, sex and the type of cancer being treated; the severity (i.e., stage) of the cancer to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease.

For example, compounds of the instant invention can be administered in a total daily dose of up to 10,000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 10,000 mg, e.g., 2,000 mg, 3,000 mg, 4,000 mg, 6,000 mg, 8,000 mg or 10,000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

For example, compounds of the instant invention can be administered in a total daily dose of up to 1,000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 1,000 mg, e.g., 200 mg, 300 mg, 400 mg, 600 mg, 800 mg or 1,000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms "intermittent" or "intermittently" as used herein means stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound of the instant invention may

be administration one to six days per week or it may mean administration in cycles (e.g. daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days.

In addition, the compounds of the instant invention may be administered according to any of the schedules described above, consecutively for a few weeks, followed by a rest period. For example, the compounds of the instant invention may be administered according to any one of the schedules described above from two to eight weeks, followed by a rest period of one week, or twice daily at a dose of 100 - 500 mg for three to five days a week. In another particular embodiment, the compounds of the instant invention may be administered three times daily for two consecutive weeks, followed by one week of rest.

Any one or more of the specific dosages and dosage schedules of the compounds of the instant invention, may also be applicable to any one or more of the therapeutic agents to be used in the combination treatment (hereinafter refered to as the "second therapeutic agent").

Moreover, the specific dosage and dosage schedule of this second therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific second therapeutic agent that is being used.

Of course, the route of administration of the compounds of the instant invention is independent of the route of administration of the second therapeutic agent. In an embodiment, the administration for a compound of the instant invention is oral administration. In another embodiment, the administration for a compound of the instant invention is intravenous administration. Thus, in accordance with these embodiments, a compound of the instant invention is administered orally or intravenously, and the second therapeutic agent can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form.

In addition, a compound of the instant invention and second therapeutic agent may be administered by the same mode of administration, i.e. both agents administered e.g. orally, by IV. However, it is also within the scope of the present invention to administer a compound of the instant invention by one mode of administration, e.g. oral, and to administer the second therapeutic agent by another mode of administration, e.g. IV or any other ones of the administration modes described hereinabove.

The first treatment procedure, administration of a compound of the instant invention, can take place prior to the second treatment procedure, i.e., the second therapeutic agent, after the treatment with the second therapeutic agent, at the same time as the treatment with the second therapeutic agent, or a combination thereof. For example, a total treatment period can be decided for a compound of the instant invention. The second therapeutic agent can be administered prior to onset of treatment with a compound of the instant invention or following treatment with a compound of the instant invention. In

addition, anti-cancer treatment can be administered during the period of administration of a compound of the instant invention but does not need to occur over the entire treatment period of a compound of the instant invention.

The instant compounds are also useful in combination with therapeutic, chemotherapeutic and anti-cancer agents. Combinations of the presently disclosed compounds with therapeutic, chemotherapeutic and anti-cancer agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, inhibitors of cell proliferation and survival signaling, bisphosphonates, aromatase inhibitors, siRNA therapeutics, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and agents that interfere with cell cycle checkpoints. The instant compounds are particularly useful when co-administered with radiation therapy.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, histone deacetylase inhibitors, inhibitors of kinases involved in mitotic progression, inhibitors of kinases involved in growth factor and cytokine signal transduction pathways, antimetabolites, biological response

modifiers, hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteosome inhibitors, ubiquitin ligase inhibitors, and aurora kinase inhibitors.

Examples of cytotoxic/cytostatic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032), Raf kinase inhibitors (such as Bay43-9006) and mTOR inhibitors (such as Wyeth's CCI-779).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteosome inhibitors include but are not limited to lactacystin and MLN-341 (Velcade).

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797. In an embodiment the epothilones are not included in the microtubule inhibitors/microtubule-stabilising agents.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-

carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in Publications WO03/039460, WO03/050064, WO03/050122, WO03/049527, WO03/049679, WO03/049678, WO04/039774, WO03/079973, WO03/099211, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98 and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. *J. Med. Chem.* 46(24):5097-5116 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone and trastuzumab.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Patent Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853,

5,290,946 and 5,356,896), atorvastatin (LIPITOR®; see U.S. Patent Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952) and cerivastatin (also known as rivastatin and BAYCHOL®; see US Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin, Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer*

*Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in U.S. Ser. Nos. 60/310,927 (filed August 8, 2001) and 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the CHK11 and CHK12 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

"Inhibitors of cell proliferation and survival signalling pathway" refer to compounds that inhibit signal transduction cascades downstream of cell surface receptors. Such agents include inhibitors of serine/threonine kinases (including but not limited to inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469), inhibitors of Raf kinase (for example BAY-43-9006 ), inhibitors of MEK (for example CI-1040 and PD-098059), inhibitors of mTOR (for example Wyeth CCI-779), and inhibitors of PI3K (for example LY294002).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possesses an $IC_{50}$ for the inhibition of COX-2 of 1μM or less as measured by cell or microsomal assays.

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of $IC_{50}$ for COX-2 over $IC_{50}$ for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Patent 5,474,995, U.S. Patent 5,861,419, U.S. Patent 6,001,843, U.S. Patent 6,020,343, U.S. Patent 5,409,944, U.S. Patent 5,436,265, U.S. Patent 5,536,752, U.S. Patent 5,550,142, U.S. Patent 5,604,260, U.S. 5,698,584, U.S. Patent 5,710,140, WO 94/15932, U.S. Patent 5,344,991, U.S. Patent 5,134,142, U.S. Patent 5,380,738, U.S. Patent 5,393,790, U.S. Patent 5,466,823, U.S. Patent 5,633,272 and U.S. Patent 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following: parecoxib, BEXTRA® and CELEBREX® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571,

CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am. J. Hum. Genet.* 61:785-789, 1997) and Kufe et al (Cancer Medicine, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 2000;164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such

as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In another embodiment, conjunctive therapy with an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is disclosed for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Patent No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with P450 inhibitors including: xenobiotics, quinidine, tyramine, ketoconazole, testosterone, quinine, methyrapone, caffeine, phenelzine, doxorubicin, troleandomycin, cyclobenzaprine, erythromycin, cocaine, furafyline, cimetidine, dextromethorphan, ritonavir, indinavir, amprenavir, diltiazem, terfenadine, verapamil, cortisol, itraconazole, mibefradil, nefazodone and nelfinavir.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with Pgp and/or BCRP inhibitors including: cyclosporin A, PSC833, GF120918, cremophorEL, fumitremorgin C, Ko132, Ko134, Iressa, Imatnib mesylate, EKI-785, Cl1033, novobiocin, diethylstilbestrol, tamoxifen, resperpine, VX-710, tryprostatin A, flavonoids, ritonavir, saquinavir, nelfinavir, omeprazole, quinidine, verapamil, terfenadine, ketoconazole, nifidepine, FK506, amiodarone, XR9576, indinavir, amprenavir, cortisol, testosterone, LY335979, OC144-093, erythromycin, vincristine, digoxin and talinolol.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

The compounds of the instant invention may also be administered in combination with γ-secretase inhibitors and/or inhibitors of NOTCH signaling. Such inhibitors include compounds described in WO 01/90084, WO 02/30912, WO 01/70677, WO 03/013506, WO 02/36555, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 2004/039800, WO 2004/039370, WO 2005/030731, WO 2005/014553, USSN 10/957,251, WO 2004/089911, WO 02/081435, WO 02/081433, WO

03/018543, WO 2004/031137, WO 2004/031139, WO 2004/031138, WO 2004/101538, WO 2004/101539 and WO 02/47671 (including LY-450139).

Inhibitors of Akt, as disclosed in the following publications; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, and including compounds of the instant invention, are also useful in combination with potassium salts, magnesium salts, beta-blockers (such as atenolol) and endothelin-a (ETa)antagonists with the goal of maintaining cardiovascular homeostasis.

Inhibitors of Akt, as disclosed in the following publications; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, and including compounds of the instant invention, are also useful in combination with insulin, insulin secretagogues, PPAR-gamma agonists, metformin, somatostatin receptor agonists such as octreotide, DPP4 inhibitors, sulfonylureas and alpha-glucosidase inhibitors with the goal of maintaining glucose homeostasis.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with PARP inhibitors.

A compound of the instant invention may also be useful for treating cancer in combination with the following therapeutic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); Darbepoetin alfa (Aranesp®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (dromostanolone®); dromostanolone propionate (masterone injection®); Elliott's B Solution (Elliott's B

Solution®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); exemestane (Aromasin®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); Rituximab (Rituxan®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); and zoledronate (Zometa®).

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating or preventing cancer that comprises administering a therapeutically effective amount of a compound of the instant invention in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of the instant invention and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

All patents, publications and pending patent applications identified are hereby incorporated by reference.

Abbreviations used in the description of the chemistry and in the Examples that follow are: AEBSF (p-aminoethylbenzenesulfonyl fluoride); BSA (bovine serum albumin); BuLi (n-Butyl lithium); $CDCl_3$ (chloroform-d); CuI (copper iodide); $CuSO_4$ (copper sulfate); DCE (dichloroethane); DCM (dichloromethane); DEAD (diethyl azodicarboxylate); DMF (N,N-dimethylformamide); DMSO (dimethyl sulfoxide); DTT (dithiothreitol); EDTA (ethylene-diamine-tetra-acetic acid); EGTA (ethylene-glycol-tetra-acetic acid); EtOAc (ethyl acetate); EtOH (ethanol); HOAc (acetic acid); HPLC (high-performance liquid chromatography); HRMS (high resolution mass spectrum); LCMS (liquid chromatograph-mass spectrometer); LHMDS (lithium bis(trimethylsilyl)amide); LRMS (low resolution mass spectrum); MeOH (methanol); MP-$B(CN)H_3$ (Macroporous cyanoborohydride); $NaHCO_3$ (sodium bicarbonate); $Na_2SO_4$ (sodium sulfate); $Na(OAc)_3BH$ (sodium triacetoxyborohydride); $NH_4OAc$ (ammonium acetate); NBS (N-bromosuccinamide); NMR (nuclear magnetic resonance); PBS (phosphate buffered saline); PCR (polymerase chain reaction); Pd(dppf) ([1,1'-bis(diphenylphosphino)ferrocene] palladium); $Pd(Ph_3)_4$ (palladium(0) tetrakis-triphenylphosphine); $POCl_3$ (phosphorous oxychloride); PS-DIEA (polystyrene diisopropylethylamine); PS-$PPh_3$ (polystyrene-triphenyl phosphine); TBAF (tetrabutylammonium fluoride); THF (tetrahydrofuran); TFA (trifluoroacteic acid); $TMSCH_2N_2$ (trimethylsilyldiazomethane) and Ac (acetyl); BOC (t-butoxycarbonyl); Bu (butyl); Cal (calculated); Calc'd (calculated); DIEA (diisopropylethylamine); DMAP (4-dimethylaminopyridine); EDC (N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide); Eq (equivalents); Et (ethyl); HOBT (hydroxybenzotriazole); IPA (isopropanol); LC/MS (liquid chromatograph-mass spectrometer); Me (methyl); MeCN (acetonitrile); NMP (N-methylpyrrolidinone); Pr (propyl); Pyr (pyridine); Sat (saturated) and Tosic (p-toluenesulfonic acid).

The compounds of this invention may be prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative Reaction Schemes below,

therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the Reaction Schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions of Formula A hereinabove.

Initial synthesis of the instant compounds are shown in Reactions Schemes I-IX. Final reactions that may be used to generate the compounds of this invention are shown in Reaction Schemes X-XIV.

Synopsis of Reaction Schemes

The following Reaction Schemes, Reaction Schemes I-IX, provide useful details for preparing the bicyclic moieties of the instant compounds.

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. As illustrated in Reaction Scheme I, a suitably substituted phenylacetylide may be reacted with copper iodide to form the corresponding copper acetylide **I-1** (see for example, Sonogashira, K.; Toda, Y.; Hagihara, N. *Tetrahedron Lett.* 1975, 4467). Intermediate **I-1** may then react with a suitably substituted electrophilic moiety to provide the asymetrically substituted **I-2**. Reaction with NBS followed by hydrolysis provides **I-3** (see for example, Yusybov, M.S.; Filimonov, V.D.; *Synthesis* 1991, *2*, 131). A variety of substituted and unsubstituted aryls and heterocyclyls may also be obtained commercially.

Reaction Scheme II illustrates the preparation of the compounds, starting with a suitably substituted **II-1**. This intermediate can be reacted with a suitably substituted amine to provide intermediate **II-2**, which can be reacted with a suitable aryl or heteroaryl diamine to provide a regioisomeric mixture of the instant compounds, which can usually be separated chromatagraphically.

Reaction Scheme III illustrates the synthesis of another bicyclic heterocyclyl.

Reaction Scheme IV illustrates the preparation of compounds, starting with a suitably substituted 4-amino-3-nitrobenzonitrile **IV-I**. This intermediate can then subjected to a microwave promoted [3+2] cycloaddition reaction to afford tetrazole **IV-II**. Alkyaltion of the acidic tetrazole with an electrophile, such as methyl iodide, delivers a 2-methyl(IV-III)/1-methyl(IV-IV) mixture of alkylated tetrazoles which are separable by column chromatography. Ra-Ni hydrogenation of **IV-III** delivers the diamine **IV-V**. Further synthesis is as described in the Reaction Schemes above.

Reaction Scheme V is illustrative for the synthesis of compounds. Friedlander cyclocondensation of a suitably substituted aryl or heteroaryl aminoaldehyde with a suitably substituted ketone gives intermediates of formula **V-1**. Conversion of the carboxylic acid functionality to an aldehyde functionality gives intermediate **V-2** and is accomplished by methods well known to someone skilled in the art. Reductive alkylation with a suitably substituted amine provides compounds of formula **V-3**.

Reaction Scheme VI illustrates an alternate synthesis of intermediate **V-2**.

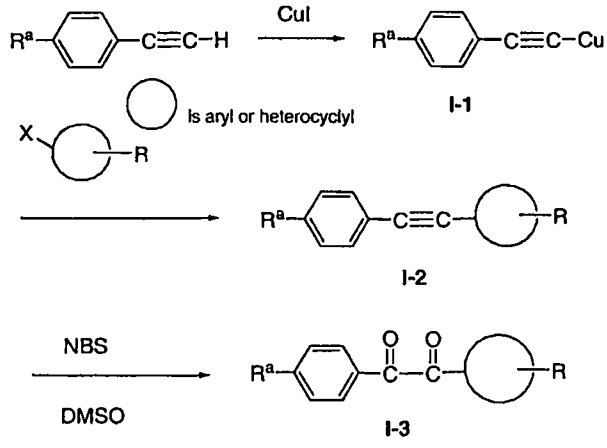
Reaction Scheme VII illustrates the synthesis of the compounds, starting with ketone **VII-1** which is prepared according to literature (Renault, O.; Dallemagne, P.; and Rault, S. *Org. Prep.*

*Proced. Int.*, 1999, *31*, 324). Condensation of **VII-1** with N,N-dimethylformamide dimethylacetal gives keto-enamine **VII-2**, which cyclizes with 2-cyanoacetamide to afford pyridone **VII-3**. Treatment of **VII-3** with phosphorus oxychloride produces chloropyridin **VII-4**. Radical bromination followed by displacement with suitably substituted amines generates amines **VII-5**. Subsequent reaction of chloronicotinonitriles **VII-5** with various bisnucleophiles provides the cyclized structures **VII-6**.

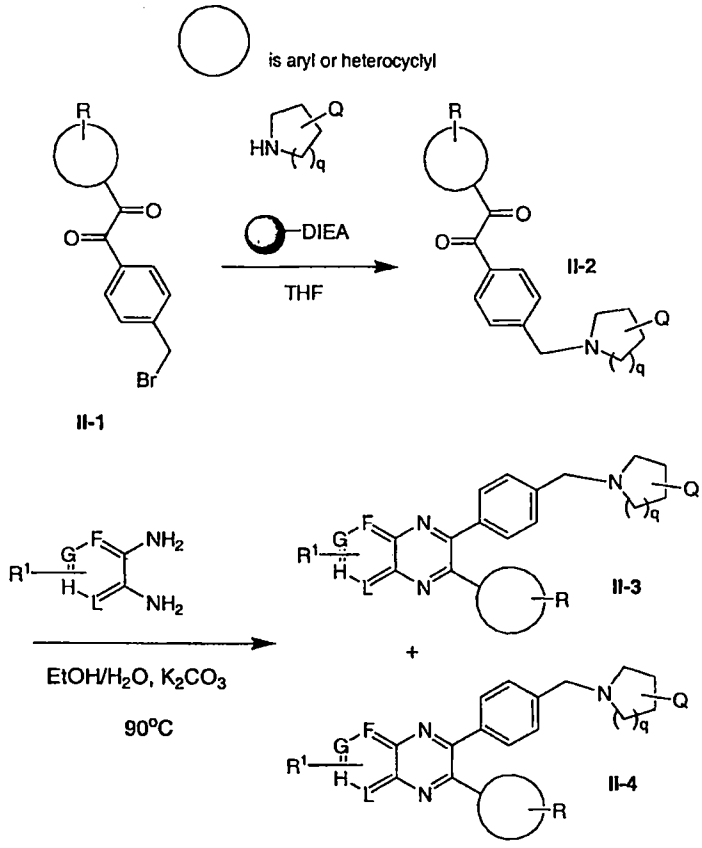
Reaction Scheme VIII illustrates the preparation of the 1,6-naphthyridin-6(5H)-one compounds. Synthesis starts with a commercially available carboxylic acid (**VIII-1**), which is converted to Weinreb amide (**VIII-2**). Reaction of amide with an aryl lithium reagent, generated through lithium-halogen exchange reaction of an aryl bromide with n-butyl lithium, provides the ketone (**VIII-3**) Condensation of this substituted ketone with 4-aminonicotinaldehyde in the presence of a base, for example, sodium hydroxide or sodium methoxide, gives the 1,6-naphthyridine (**VIII-4**). The R substituent on the phenyl can be a functional group, such as, a (silyl)protected hydroxymethyl, the masked aldehyde (i.e. acetal), or a carboxylic acid. This material can be converted to the requisite aldehyde **VIII-4**. When the R group is hydroxymethyl, oxidation with a reagent such as activated manganese dioxide gives the aldehyde **VIII-4**. When R is an acetal, mild acid hydrolysis gives the aldehyde. Reduction of the carboxylic acid group via reduction of a mixed anhydride with a borohydride also gives the aldehyde **VIII-4**. This aldehyde can then undergo reductive amination with a diverse array of amines, for example, a 4-subtituted piperidine, and a borohydride to provide 1,6-naphthyridin-5(H)-ones (**VIII-5**). Treatment of (**VIII-5**) with pyridinium hydrochloride at 150 °C furnishes the final product (**VIII-6**).

Reaction Scheme IX illustrates an alternate strategy of introducing heterocycles at the C3-position. It starts with commercially available dichloro benzopyrazine, which can be coupled to an aryl boronic acid in the presence of a palladium catalyst (Suzuki reaction). Then a repeat of this reaction with another heterocyclic boronic acid provides the final product, under the same reaction conditions.

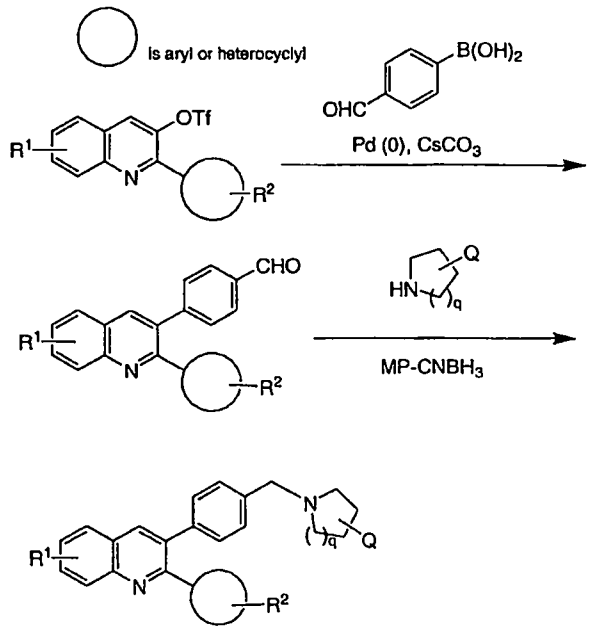
Reaction Scheme I



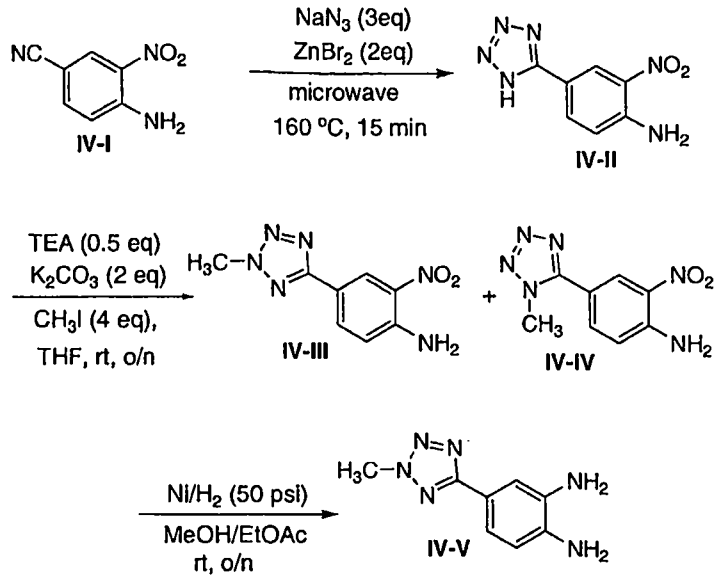
Reaction Scheme II



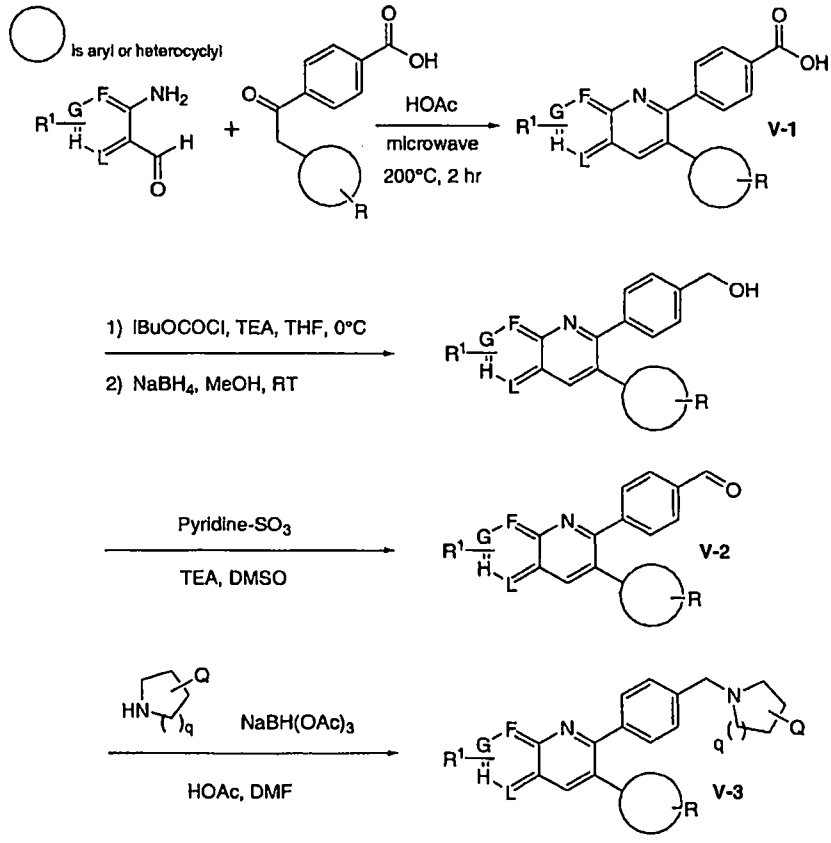

Reaction Scheme III



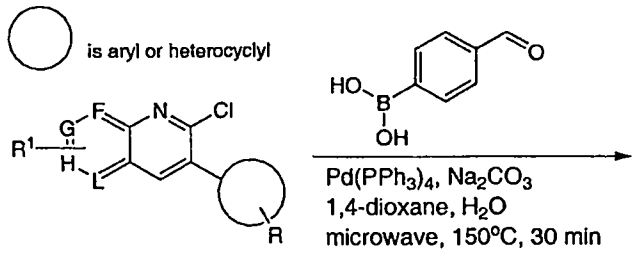
Reaction Scheme IV

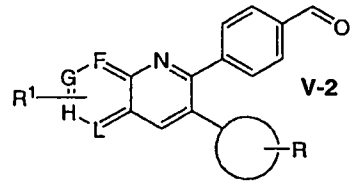



Reaction Scheme V



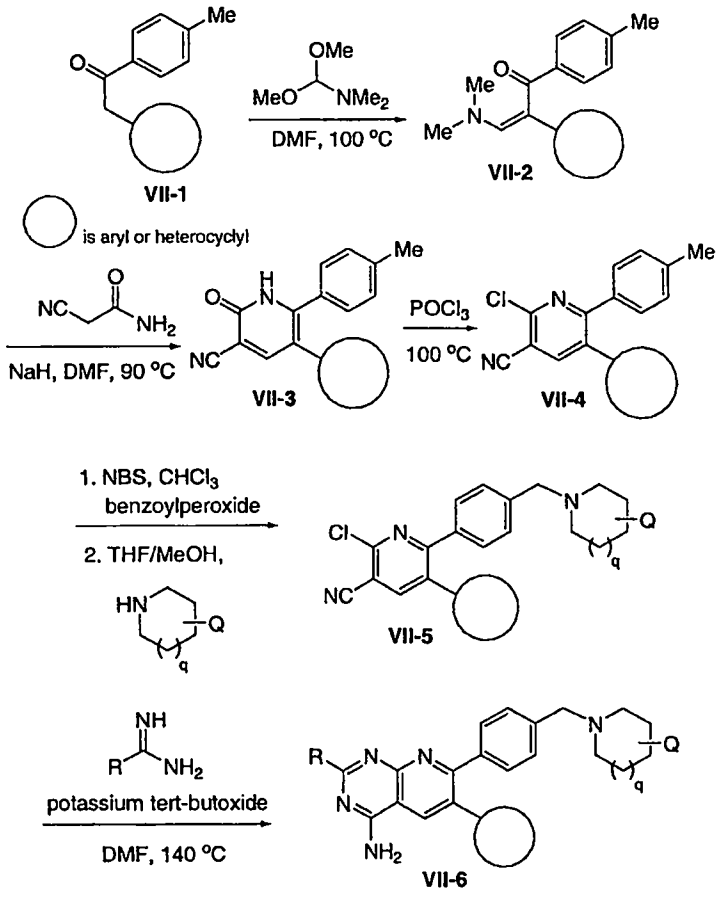
Reaction Scheme VI



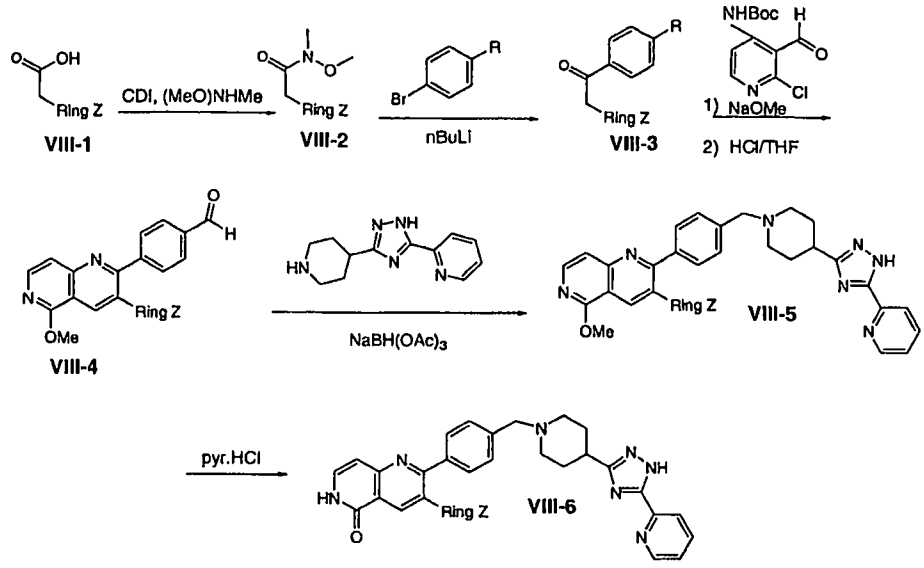




V-2

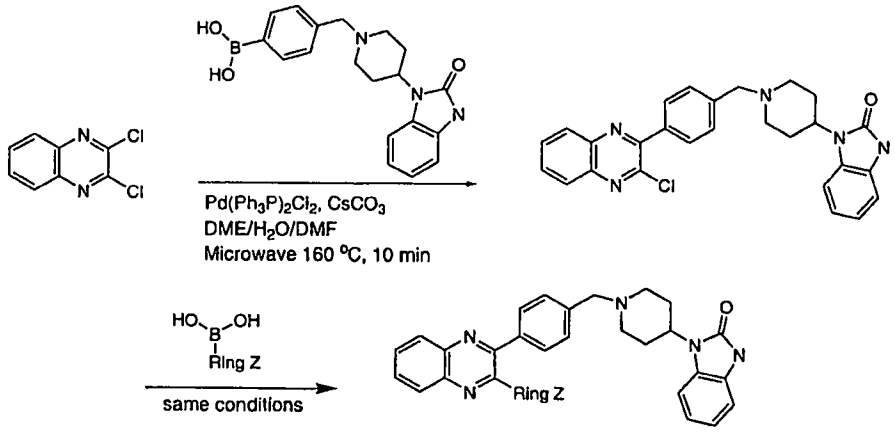
Reaction Scheme VII



Reaction Scheme VIII




Reaction Scheme IX




Final Synopsis of Reaction Schemes

The following Reaction Schemes, Reaction Schemes X-XIV, provide useful details for preparing the tricyclic moieties of the instant compounds.

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures. Treatment of a suitably substituted aryl or heteroaryl intermediate **X-1** with $POCl_3$ gives intermediates of formula **X-2**. Conversion of the chloride functionality to a hydrazide functionality gives intermediate **X-3** and is accomplished by methods well known to someone skilled in the art. Cyclization with a suitably diimidazole precusor provides compounds of formula **X-4**.

Reaction Scheme XI illustrates an alternate synthesis of compounds of formula **X-4**.

Reaction Scheme XII illustrates synthesis of compounds of formula **XII-2**. Condensation of **X-3** with appropriate trimethoxychloroacetate gives chloromethyl intermediate **XII-1**, which, via a nucleophilic displacement, affords structure **XII-2**.

Reaction Scheme XIII illustrates the preparation of the triazolonaphthyridine compounds. Synthesis starts with literature/patent known naphthyridone (**XIII-1**), which is converted to naphthyridine chloride (**XIII-2**) after treatment of $POCl_3$ under reflux condition. Reaction of the latter compound with neat hydrazine, and under reflux condition, provides the hydrazide (**XIII-3**) which serves as a key intermediate for the synthesis of triazolonaphthyridine compounds. Conversion of this hydrazide (**XIII-4**) to the requisite triazolonaphthyridine compounds under indicated conditions complete the planned synthesis. The R substituent on the triazolo moiety can be a functional group, such as, an amino group, an oxo group or a thiol group.

Reaction Scheme XIV illustrates an alternate strategy of introducing the triazolo moiety at the left-hand portion of the molecule. It starts with previously synthesized intermediate hydrazide (**XIII-3**) which can be treated with a trimethoxy orthoacetate to furnish the desired final product, tiazolonaphthridine compounds (**XIV-1**). The R substituent on the triazolo moiety can be a functional group, such as, a proton, a simple alkyl group, a chloromethyl group or a functionalized alkyl group.

Reaction Scheme **XV** illustrates the synthesis of compounds of formula **XV-1** using three different reductive amination methods to introduce a primary amine at the benzylic position. The methods are also applicable to other aldehydes such as compounds of formula **XVII-1**.

Reaction Scheme **XVI** illustrates the synthesis of compounds of formula **XVI-2** using a variant of the conditions for the cyclocondensation shown in reaction Scheme **VIII**. Use of an aprotic solvent and a base gives access to chloronaphthyridines of structure **XVI-2**.

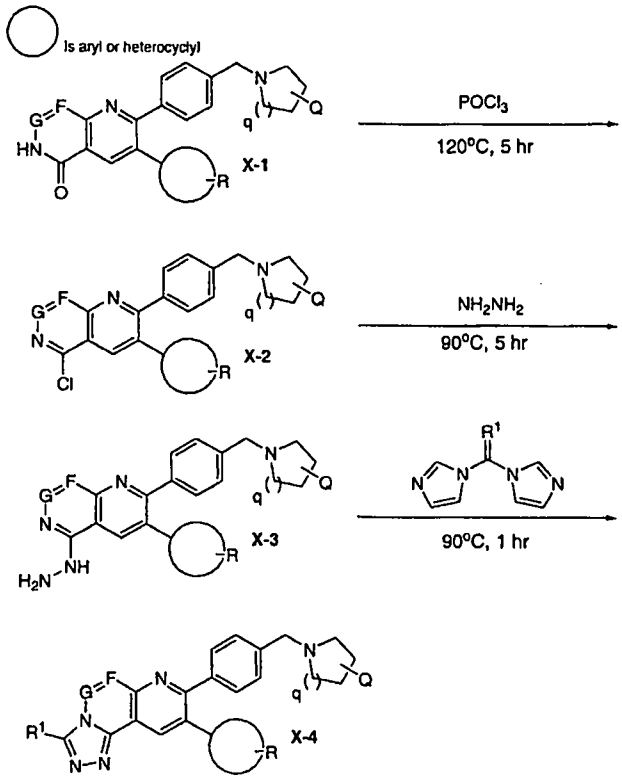
Reaction Scheme **XVII** illustrates the synthesis of compounds of formula **XVII-4**. In this case a methyl substituent is introduced at the benzylic position via sulfinamide **XVII-2**. Other substituents can be introduced using organometallic reagents such as Grignard reagents. The t-butylsulfinimide can be cleaved using an acid such as HCl to give the amine.

Reaction Scheme **XVIII** illustrates the synthesis of compounds of formula **XVIII-2** as a variant of the triazole synthesis described in Reaction Scheme **XI**. In this case the hydrazine **XVIII-1** is coupled to a carboxylic acid and the intermediate acylhydrazine is cyclized to the fused triazole under acid catalysis.

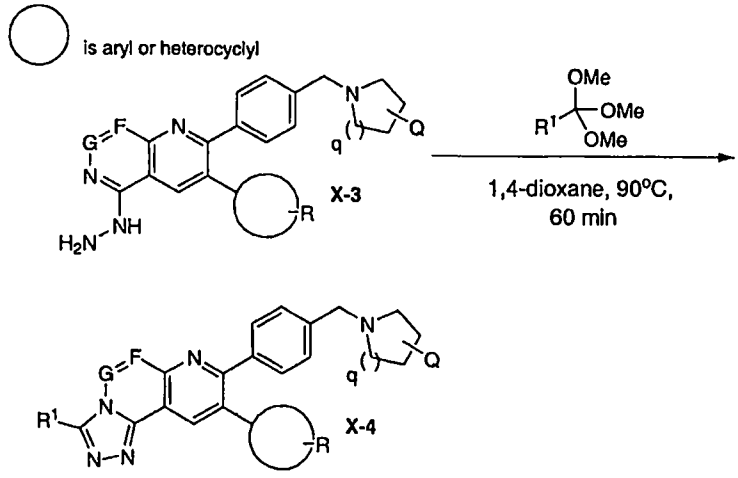
Reaction Scheme **XIX** illustrates the synthesis of compounds of formula **XIX-2** in which the cyclopropylamine is synthesized from the nitrile **XIX-1**.

Reaction Scheme **XX** illustrates the synthesis of compounds of formula **XX-2** from amines of formula **XX-1** under standard reductive amination conditions.

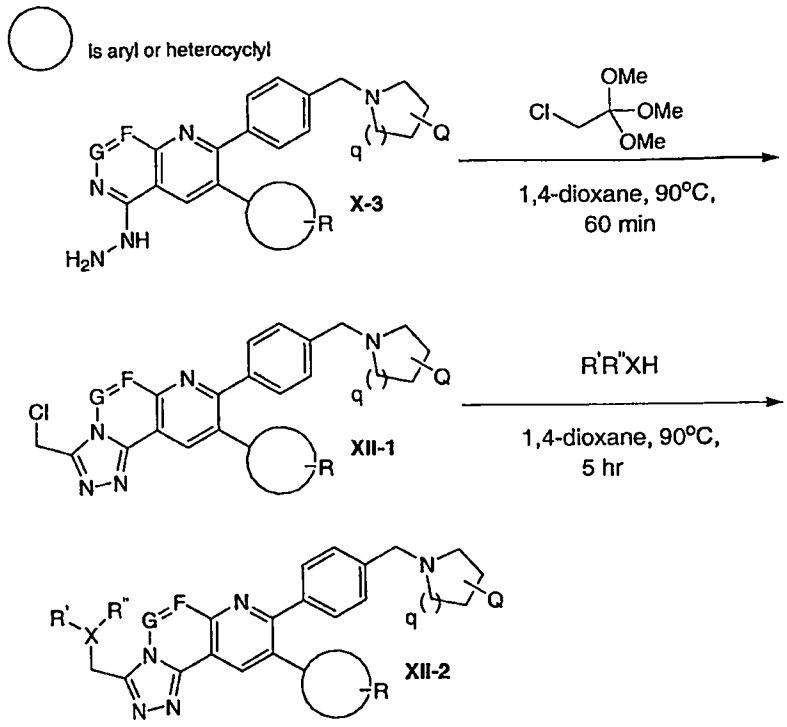
Reaction Scheme X



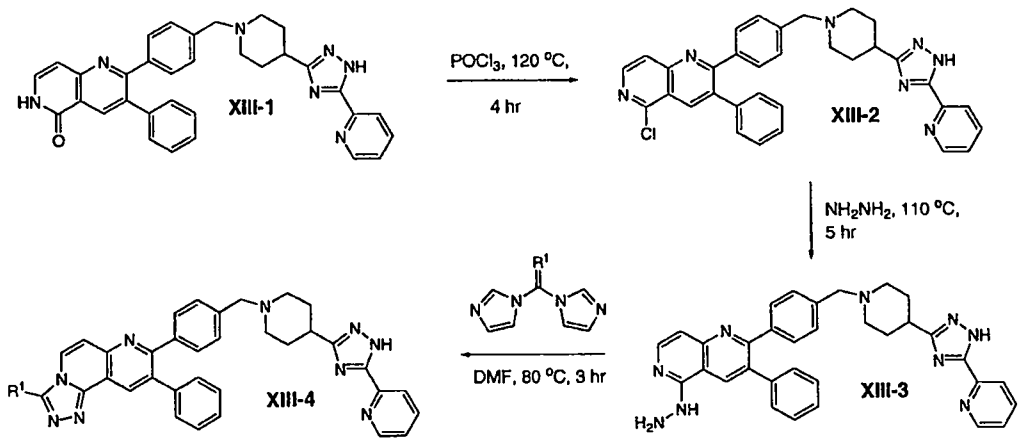

Reaction Scheme XI



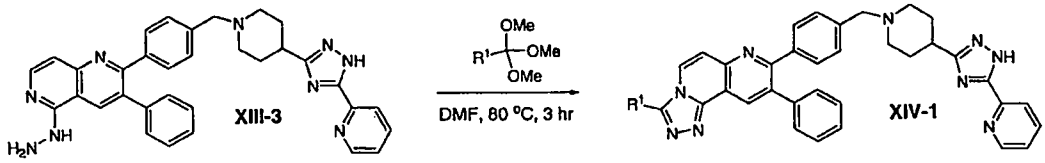
Reaction Scheme XII



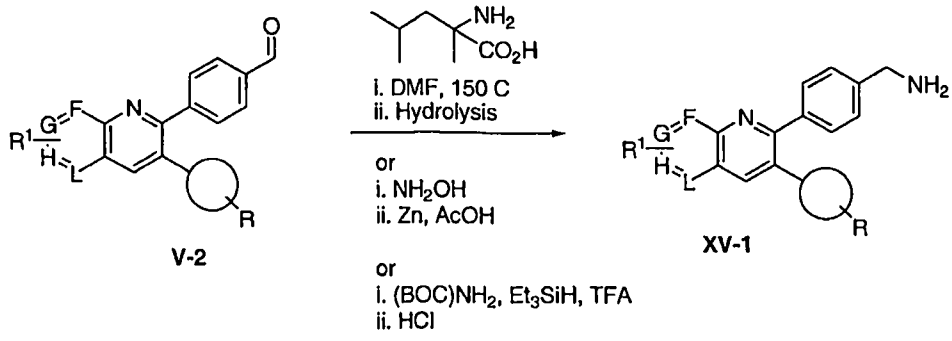

Reaction Scheme XIII



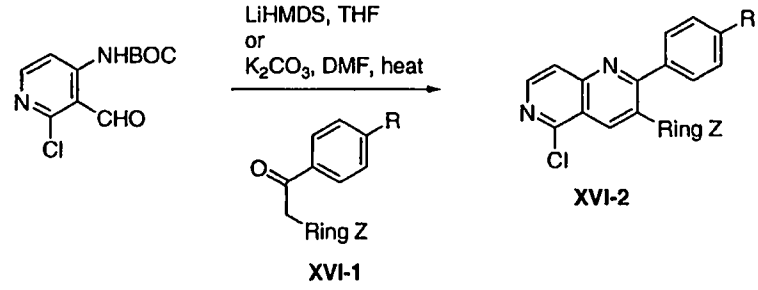

Reaction Scheme XIV



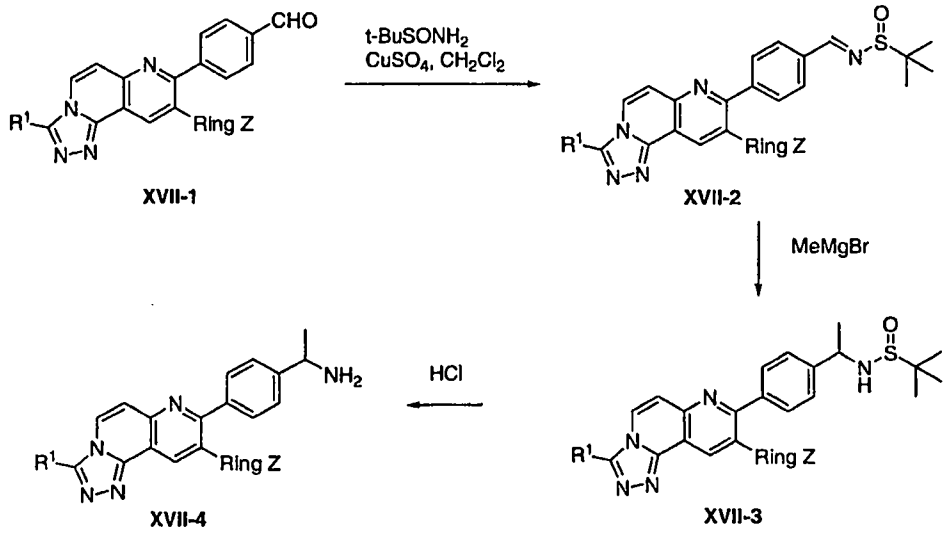
Reaction Scheme XV



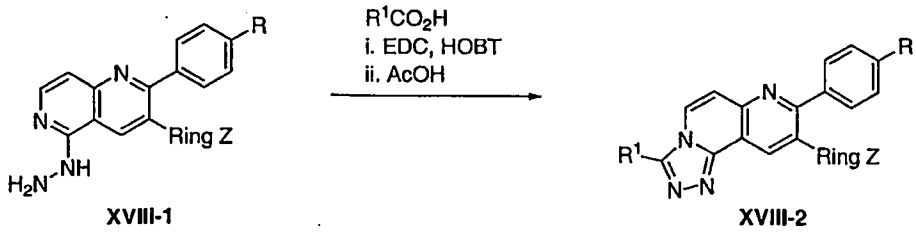

Reaction Scheme XVI




Reaction Scheme XVII

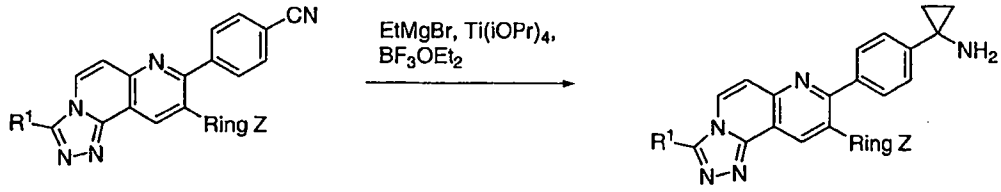


Reaction Scheme XVIII



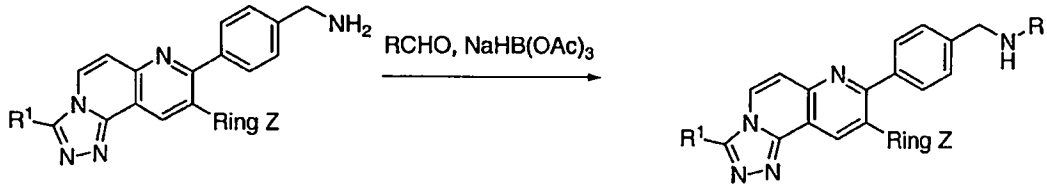

XVIII-1 XVIII-2

Reaction Scheme XIX




XIX-1 XIX-2

Reaction Scheme XX

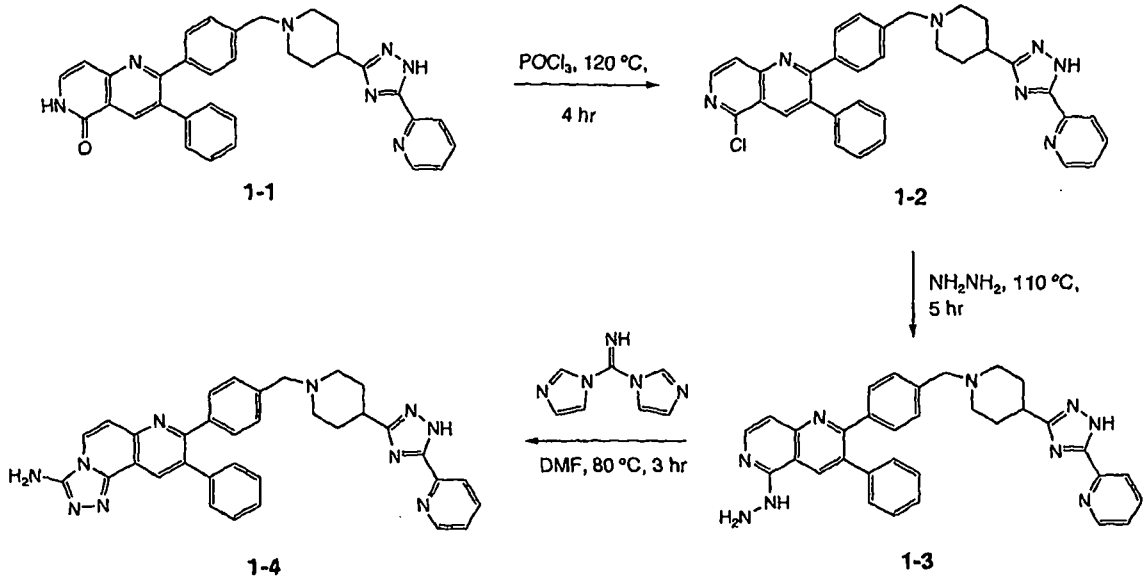



XX-1 XX-2

EXAMPLES

Examples and schemes provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and do not limit the reasonable scope thereof.

SCHEME 1




9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (1-4)

5-chloro-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl} phenyl)-1,6-naphthylridine (1-2)

A 25 mL RB flask with a stirring bar was charged with 3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazo-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridin-5(6H)-one (0.86 g, 1.6 mmol), followed by anhydrous $POCl_3$ (8 mL). The mixture was heated to 120°C and stirred under reflux for 4 hours. After the reaction was cooled to room temperature, the reaction mixture was carefully added to a mixture of cold saturated $NaHCO_3$ aqueous solution (20 mL) and EtOAc (20 mL). The PH of the aqueous layer was maintained at around PH 8-9 throughout the quenching process. The aqueous solution was further extracted twice with EtOAc (15 mL) and the residue was washed with MeOH (20 mL). The organic phases were combined and concentrated *in vacuo* to give 5-chloro-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthylridine (**1-2**) (900 mg). The crude material was used directly in the next step without further purifications.

5-hydrazino-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl] methyl}phenyl)-1,6-naphthyridine (1-3)

A 25 ml RB flask with a stirring bar was charged with 5-chloro-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthylridine (**1-2**) (900 mg, 1.6 mmol), followed by anhydrous $NH_2NH_2$ (8 mL). The suspension was heated to 110°C and stirred under reflux for 5 hours. After the reaction was cooled to room temperature, the reaction mixture was

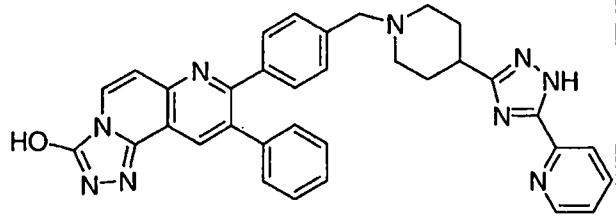
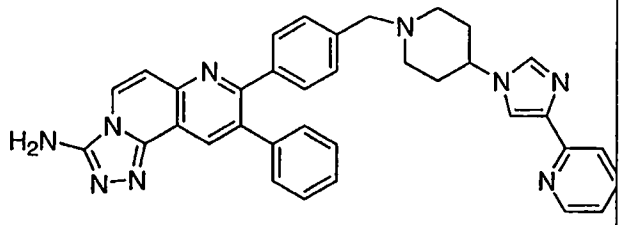
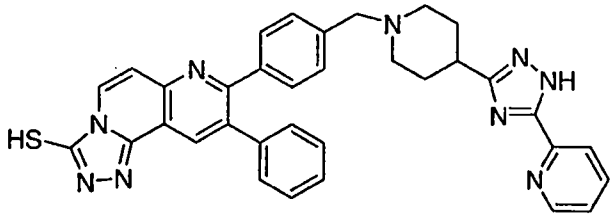
concentrated *in vacuo* to give a yellowish powder (900 mg). The crude product was taken to the next step without further purification.

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**1-4**)

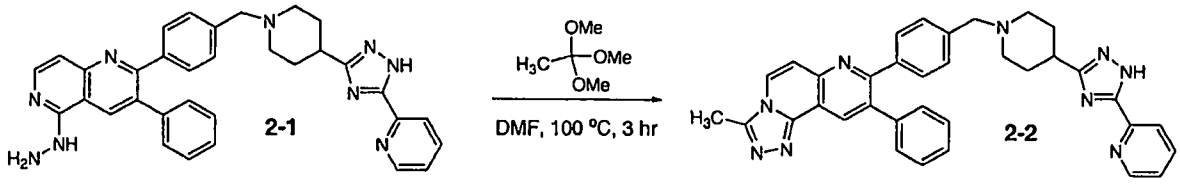
To 5-hydrazino-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (**I-3**) (70 mg, 0.126 mmol) in DMF (1.5 mL) was added literature known 1,1-di-1H-imidazol-1-ylmethanimine (102 mg, 0.633 mmol). The reaction mixture was stirred at 85°C for 4 hours, concentrated *in vacuo*, and chromatographed to furnish the desired 9-phenyl-8-(4-{[40(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]emthyl}phenyl}[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**1-4**) (46 mg) as its trifluoroacetic acid salt. $^1$H NMR: (500MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.74 (d, *J*= 4.3 Hz, 1H), 8.29-8.27 (m, 2 H), 8.19 (m, 1H), 7.67 (m, 1H), 7.54-7.53 (m, 2H), 7.48-7.46 (m, 2H), 7.47 (d, *J*= 7.7 Hz , 1H), 7.34-7.26 (m, 5H), 4.43 (s, 2H), 3.65 (br d, *J*= 10.9 Hz, 2H), 3.46 (br s, 1 H), 3.27-3.19 (m, 2H), 2.50-2.42 (m, 2H), 2.10-2.06 (m, 2H).

The following compounds in Table 1 were prepared in a similar manner as shown in Scheme 1 and as shown in the Reaction Schemes.

Table 1

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| 1-5 |  | 9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol | 579.3 |
| 1-6 |  | 9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine | 577.3 |
| 1-7 |  | 9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-thiol | 595.2 |

SCHEME 2



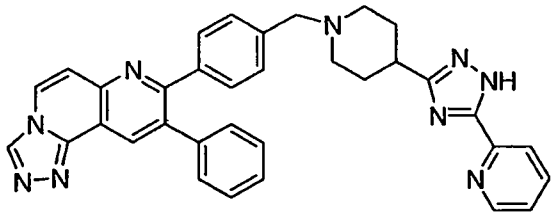
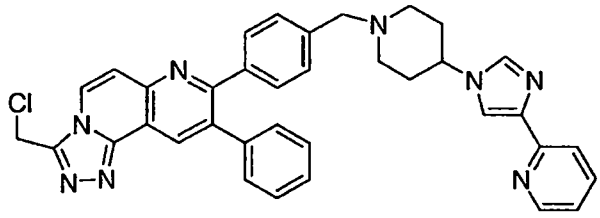
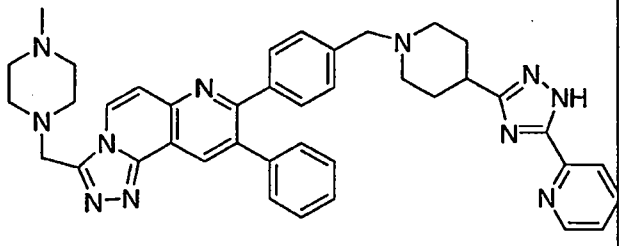

3-methyl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (2-2)

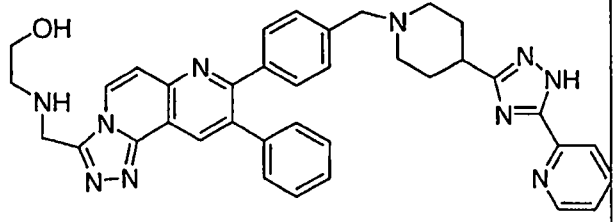
To 5-hydrazino-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (2-1) (55 mg, 0.101 mmol) in DMF (1.0 mL) was added trimethyl orthoacetate (0.63 mL, 5.04 mmol). The reaction mixture was stirred at 100°C for 3 hours, and then concentrated *in vacuo*, and chromatographed to furnish the desired 3-methyl-9-phenyl-8-(4-{[4-(5-

pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**2-2**) (28 mg) as its trifluoroacetic acid salt. $^1$H NMR: (500MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.65 (d, *J*= 6.4 Hz, 1H), 8.33 (d, *J*= 7.5 Hz, 1H), 8.11 (d, *J*= 7.8 Hz, 1H), 7.92 (t, *J*= 7.8 Hz, 1H), 7.49-7.41 (m, 3 H), 7.36-7.30 (m, 8H), 3.61 (s, 2H), 3.02-3.00 (m, 2H), 3.00-2.84 (m, 1 H), 2.25-2.21 (m, 2H), 2.10-1.83 (m, 4H), 1.97 (s, 3H).

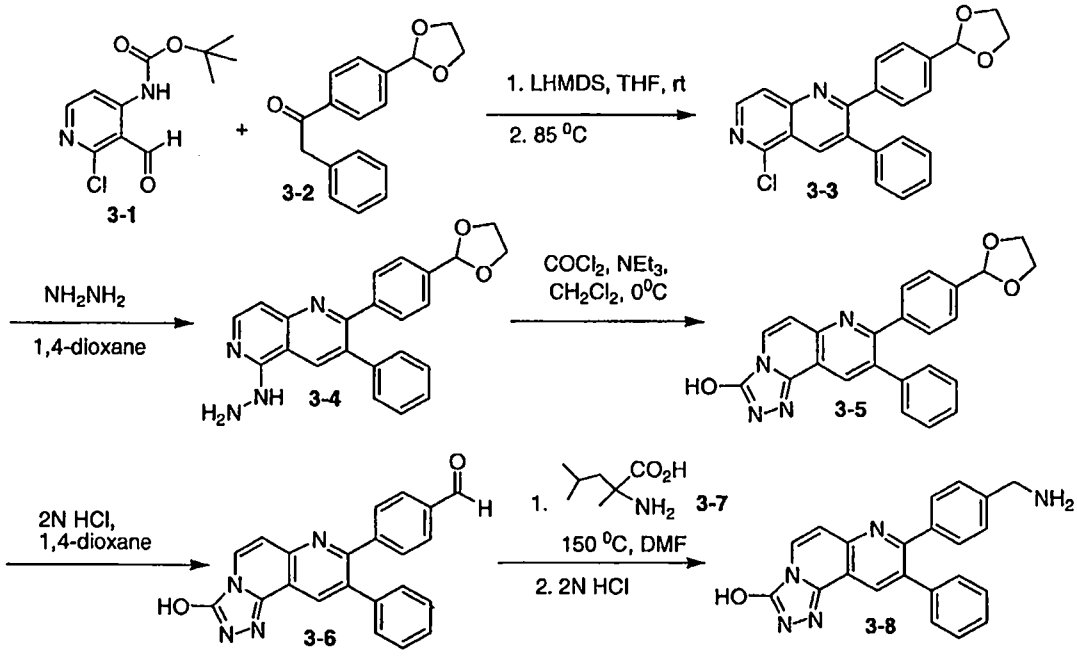
The following compounds in Table 1 were prepared in a similar manner as shown in Scheme 2 and as shown in the Reaction Schemes:

Table 2

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **2-3** |  | 9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 563.3 |
| **2-4** |  | 3-(chloromethyl)-9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 610.2 |
| **2-5** |  | 3-[(4-methylpiperazin-1-yl)methyl]-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 675.4 |

| | | | |
|---|---|---|---|
| 2-6 |  | 2-({[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}amino)ethanol | 636.3 |

SCHEME 3




8-(4-Aminomethyl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (3-8)

STEP A: tert-Butyl (2-chloro-3-formylpyridin-4-yl)carbamate (3-1)

A solution of 4-amino-2-chloropyridine (1.28 gm, 10 mmol) and di-tert-butyl dicarbonate (2.21 gm, 10.1 mmol) in THF (20 mL) was cooled to 0°C and a solution of 1M lithium bis(trimethylsilyl)amide in THF ( 20 mL, 20 mmol) was added slowly maintaining the temperature below 0°C. The reaction was allowed to warm to room temperature over one hour and then quenched by the addition of 1.5 N aqueous ammonium chloride (15 mL). After stirring for several hours the reaction was extracted into ethyl acetate, washed with brine, the organic layer dried ($Na_2SO_4$), filtered and evaporated. The residue was triturated with diethyl ether give pure tert-butyl (2-chloropyridin-4-yl)carbamate. The mother liquors were chromatographed on silica gel eluting with 25 – 45% ethyl acetate/ hexane to afford more product.

A solution of tert-butyl (2-chloropyridin-4-yl)carbamate (1.14 gm, 5 mmol) in dry THF (20 mL) was cooled to -70°C under an inert atmosphere and 1.7 M t-butyl lithium/pentane (8 mL, 13.5 mmol) was slowly added. The reaction was stirred for two hours and then dry DMF (1.2 mL, 15.5 mmol) was added. The reaction was allowed to slowly warm to room temperature over a three hour period. The reaction mixture was quenched with 3 N HCl (12 mL) and diluted with diethyl ether. The ether layer was washed with aqueous $NaHCO_3$, dried (over $Na_2SO_4$), filtered and evaporated. The residue was triturated with cold diethyl ether to give pure t-butyl (2-chloro-3-formylpyridin-4-yl)carbamate. The mother liquors were chromatographed on silica gel eluting with 15-20% ethyl acetate/hexane to give additional product. 1H-NMR(500 MHz, $CDCl_3$): δ11.0 (1H, br s), 10.52 (1H, s), 8.38 (1H, d, J= 6 Hz), 8.31 (1H, d, J= 6 Hz), 1.54 (9H, s); m/e (m+1): 257.2.

STEP B: 1-[4-(1,3-Dioxolan-2-yl)phenyl]-2-phenylethanone (3-2)

To a solution of 4-cyanobenzaldehyde (20.0 g, 152.5 mmol) and ethylene glycol (25.5 mL, 457.5 mmol) in toluene (250 mL) was added p-toluenesulfonic acid (300 mg). The flask was equipped with a Dean-Stark trap and the mixture heated to reflux. After 5 hr the mixture was concentrated. The residue was taken up in ethyl acetate and washed with saturated $NaHCO_3$, water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 4-(1,3-dioxolan-2-yl)benzonitrile as a clear oil which solidified under vacuum: 1H-NMR (500 MHz, $CDCl_3$): δ7.67 (2 H, d, J = 8.06 Hz), 7.59 (2 H, d, J = 8.30 Hz), 5.85 (1H, s), 4.13-4.05 (4H, m).

To a solution of 4-(1,3-dioxolan-2-yl)benzonitrile (5.0 g, 28.54 mmol) in anhydrous THF (100 mL) was added benzyl magnesium chloride (36 mL, 20% wt solution in THF, 43 mmol) slowly at 0°C. After one hour the mixture was warmed to room temperature. After four hours the mixture was cooled to 0°C and quenched with saturated $NH_4Cl$. The mixture was warmed to room temperature and extracted with ethyl acetate (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography(10% ethyl acetate/hexanes) gave 1-[4-(1,3-dioxolan-2-yl)phenyl]-2-phenylethanone as a pale yellow solid: 1H-NMR (500 MHz, $CDCl_3$): δ8.02 (2 H, d, J = 8.30 Hz,), 7.57 (2 H, d, J = 8.30 Hz,), 7.38-7.24 (%H, m), 5.86 (1H, s), 4.29 (2H, s), 4.28-4.09 (4H, m).

STEP C: 5-Chloro-2-(4-[1,3]dioxolan-2-yl-phenyl)-3-phenyl-[1,6] naphthyridine (3-3)

To a solution of tert-butyl (2-chloro-3-formylpyridin-4-yl) carbamate (**3-1**, 30.5 g, 118.9 mmol) and 1-[4-(1,3-dioxolan-2-yl)phenyl]-2-phenylethanone (**3-2**, 29.0 g, 108.1 mmol) in anhydrous THF (300 mL) at room temperature was added LHMDS (1M in THF, 248 mL) in a stream. The reaction mixture was stirred at room temperature overnight and then it was refluxed for 24 hr. It was cooled and concentrated to a syrup and treated with $NaHCO_3$ (saturated, 50 mL) and water (300 mL) to form a solid which was collected via filtration. The solid was dried, washed with ether and further dried with toluene azeotropically to give the title compound. LRMS m/z (M+1) Calcd: 389.1, found 389.1.

STEP D: [2-(4-[1,3]Dioxolan-2-yl-phenyl)-3-phenyl-[1,6]naphthyridin-5-yl]-hydrazine (3-4)

A suspension of 5-chloro-2-(4-[1,3]dioxolan-2-yl-phenyl)-3-phenyl-[1,6]naphthyridine (**3-3**, 5.2 g, 13.4 mmol) and anhydrous hydrazine (5 mL) in anhydrous 1,4-dioxane (15 mL) was heated at 100°C in a microwave reactor for 5 min. The reaction mixture was cooled, concentrated and dried with toluene azotropically to give the title compound as a solid. LRMS m/z (M+1) Calcd: 385.2, found 385.3.

STEP E: 8-(4-[1,3]Dioxolan-2-yl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (**3-5**)

To a solution of [2-(4-[1,3]dioxolan-2-yl-phenyl)-3-phenyl-[1,6]naphthyridin-5-yl]-hydrazine (**3-4**, 5.3 g, 13.8 mmol) in $CH_2Cl_2$ (anhydrous, 40 mL) at 0°C was added triethylamine (9.7 mL, 68.9 mmol) followed by a rapid addition of phosgene in toluene (2M, 7.6 mL). After stirring for 10 min at room temperature, the mixture was concentrated and water (30 mL) was added. The solid was collected and dried with toluene azeotropically to give the title compound which was used for the next step without further purification. LRMS m/z (M+1) Calcd: 411.1, found 411.2.

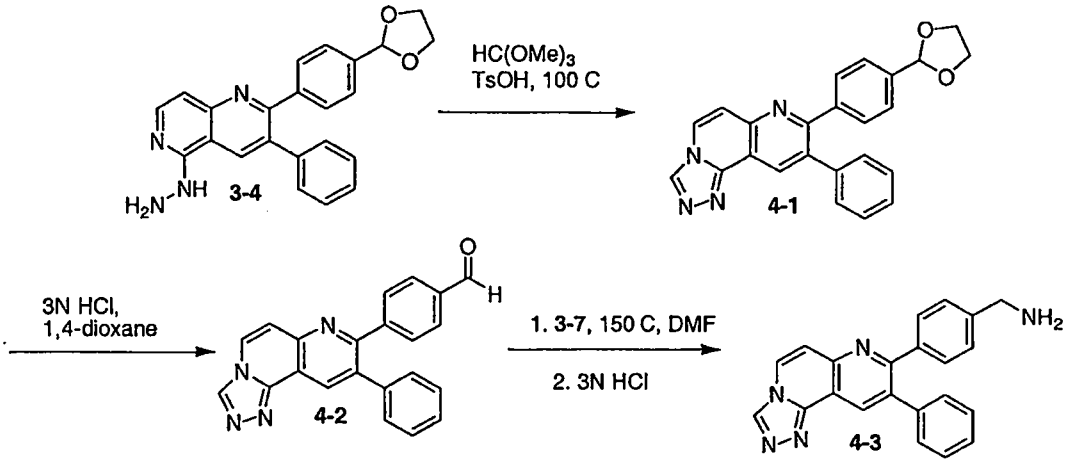
STEP F: 4-(3-Hydroxy-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzaldehyde (**3-6**)

A suspension of 8-(4-[1,3]dioxolan-2-yl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (**3-5**, 2.7 g, 6.6 mmol) in dioxane (20 mL) and 2N HCl (20 mL) was stirred at room temperature for 20 min. It was concentrated to remove most dioxane at 25°C. The residue was poured into ice cold water to give a brown solid which was collected via filtration and dried with toluene azeotropically to give the title compound. LRMS m/z (M+1) Calcd: 367.1, found 367.1.

STEP G: 8-(4-Aminomethyl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol (**3-8**)

A suspension of 4-(3-hydroxy-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzaldehyde (**3-6**, 2.4 g, 6.6 mmol) and 2-amino-2,4-dimethylpentanoic acid (**3-7**, 1.9 g, 13.1 mmol) in DMF (25 mL) was heated at 150°C for 20 min. The reaction mixture was cooled, diluted with dioxane (50 mL) and 2N HCl (50 mL) and heated at 100°C for 30 min. The mixture was cooled and purified via reverse phase HPLC (0-60% acetonitrile/water) to give, upon evaporation of the solvent, the title compound as a yellow solid. HRMS m/z (M+1) Calcd: 368.1506, found 368.1504.
$^1$H-NMR ($CD_3OD$) δ 8.72 (s, 1 H), 7.98 (d, 1 H), 7.52 (d, 2 H), 7.46(d, 2 H), 7.24-7.38(m, 5 H), 7.12 (d, 1 H), 4.14 (s, 2 H).

SCHEME 4




1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl] methanamine (**4-3**)

STEP A: 8-[4-(1,3-Dioxolan-2-yl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**4-1**)

To a solution of [2-(4-[1,3]dioxolan-2-yl-phenyl)-3-phenyl-[1,6]naphthyridin-5-yl]-hydrazine(**3-4**, 1.6 g, 4.2 mmol) and toluenesulfonic acid monohydrate (79 mg, 0.4 mmol) in 3:1 toluene:MeOH (16 mL) was added trimethyl orthoformate (0.58 mL, 12.5 mmol). The mixture was heated to 100°C in a microwave reactor for 1 hr. The reaction mixture was then concentrated *in vacuo*. The solid was collected and dried with toluene azeotropically to give the title compond which was used for next step without further purification. LRMS m/z (M+1) Calcd: 395.1, found 395.2.

STEP B: 4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl) benzaldehyde (**4-2**)

A suspension of 8-[4-(1,3-dioxolan-2-yl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**4-1**, 0.80 g, 2.0 mmol) in dioxane (10 mL) and 3N HCl (10 mL) was stirred at room temperature for 15 min. The mixture was concentrated at 25°C to remove most of the dioxane. The residue was poured into ice cold water to give a brown solid which was collected via filtration and dried with toluene (x2) azeotropically the give the title compound. LRMS m/z (M+1) Calcd: 351.1, found 351.2

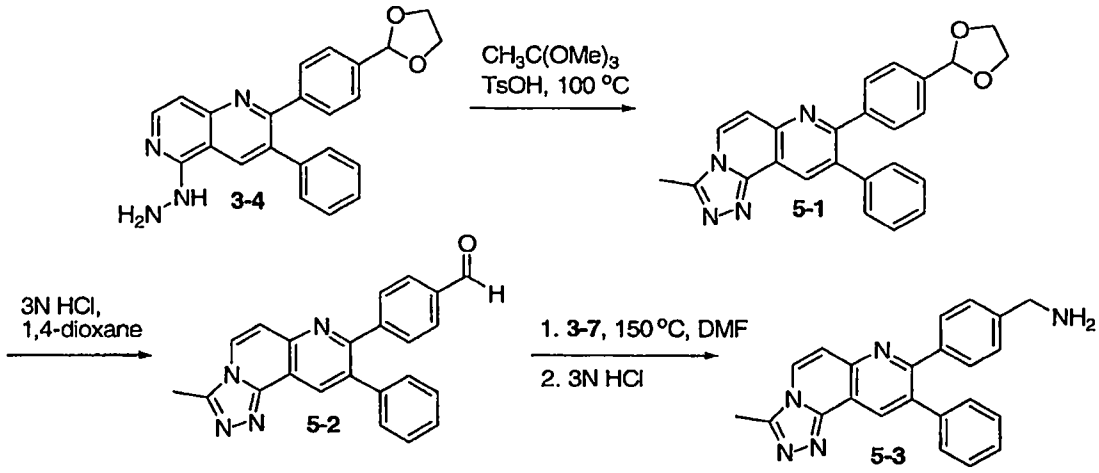
STEP C: 1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl] methanamine (**4-3**)

A suspension of 4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzaldehyde (**4-2**, 0.80 g, 2.3 mmol) and 2-amino-2,4-dimethylpentanoic acid (**3-7**, 0.340 g, 2.3 mmol) in DMF (10 mL) was heated at 150°C for 30 min. The reaction mixture cooled and the solvent was removed *in vacuo*. The crude residue was dissolved in 3N HCl (8 mL) and was heated at 100°C for 30 min. The

mixture was cooled and purified via reverse phase HPLC (5-65% acetonitrile/water over 15 min) to give, upon evaporation of the solvents, the title compound as a yellow solid.

$^1$H-NMR ($CD_3OD$) δ 9.60 (s, 1 H), 8.98 (s, 1 H), 8.73 (d, 1 H), 7.75 (d, 1 H), 7.60 (d, 2 H), 7.46 (d, 2 H), 7.39-7.36 (m, 5 H), 4.15 (s, 2H).

SCHEME 5




4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine (5-3)

STEP A: 8-[4-(1,3-Dioxolan-2-yl)phenyl]-3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (5-1)

To a solution of [2-(4-[1,3]dioxolan-2-yl-phenyl)-3-phenyl-[1,6]naphthyridin-5-yl]-hydrazine(**3-4**, 0.35 g, 0.91 mmol) and toluenesulfonic acid monohydrate (17 mg, 0.09 mmol) in 3:1 toluene:MeOH (4 mL) was added trimethyl orthoacetate (0.157 mL, 1.23 mmol). The mixture was heated to 100°C in a microwave reactor for 75 min. The reaction mixture was then concentrated *in vacuo*. The solid was collected and dried with toluene azeotropically to give the title compond which was used for next step without further purification. LRMS m/z (M+1) Calcd: 409.2, found 409.2.

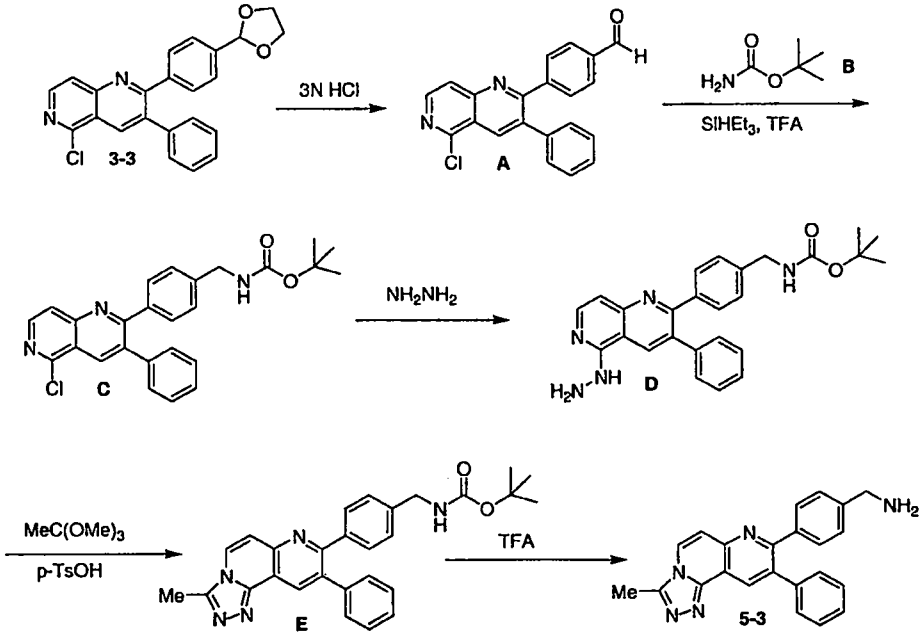
STEP B: 4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl) Benzaldehyde (5-2)

A suspension of 8-[4-(1,3-dioxolan-2-yl)phenyl]-3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**5-1**, 0.30 g, 0.73 mmol) in dioxane (5 mL) and 3N HCl (5 mL) was stirred at room temperature for 15 min. The mixture was concentrated at 25°C to remove most of the dioxane. The residue was poured into ice cold water to give a brown solid which was collected via filtration and dried with toluene (x2) azeotropically the give the title compound. LRMS m/z (M+1) Calcd: 365.1, found 365.2.

STEP C: 4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine (5-3)

A suspension of 4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzaldehyde (**13**, 0.25 g, 0.69 mmol) and 2-amino-2,4-dimethylpentanoic acid (**3-7**, 0.101 g, 0.69 mmol) in DMF (3 mL) was heated at 150°C for 30 min. The reaction mixture cooled and the solvent was removed *in vacuo*. The crude residue was dissolved in 3N HCl (2.5 mL) and was heated at 100°C for 30 min. The mixture was cooled and purified via reverse phase HPLC (5-65% acetonitrile/water over 15 min) to give, upon evaporation of the solvents, the title compound as a yellow solid. HRMS m/z (M+1) Calcd: 366.1713, found 366.1715.

SCHEME 5 (ALTERNATE SYNTHESIS)




4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzyl amine (**5-3**)

STEP A: 4-(5-Chloro-3-phenyl-[1,6]naphthyridin-2-yl)-benzaldehyde (**A**)

To a solution of **3-3** (5.0g, 12.9mmol) in 1,4-dioxane (30mL) at 0°C was added 8.5mL of 3NHCl (25.7mmol). The mixture was allowed to warm up to room temperature and stirred for 1.3 hr. The reaction was quenched by $NaHCO_3$ (sat) until pH=7-8. The mixture was extracted by EtOAc (x3). The combined organic layers was washed with brine and dried over $MgSO_4$ and concentrated to afford a yellow solid as the desired product **A**. LC/MS found: M+1=345.1

STEP B: [4-(5-Chloro-3-phenyl-[1,6]naphthyridin-2-yl)-benzyl]-carbamic acid *tert*-butyl ester (**C**)

To a solution of **A** (2.8g, 8.1mmol) and **B** (1.1g, 8.9mmol) in 15mL anhydrous MeCN was added triethylsilane (8.5g, 73mmol) followed by trifluoroacetic acid (3.7g, 32.5mmol). The mixture was stirred at room temperature for 3 hrs. The mixture was then poured into aqueous sodium bicarbonate solution (30mL) and extracted by EtOAc (x3). The combined organic layers were washed by brine and

dried over $MgSO_4$. Upon removal of the solvent, the residue was purified via flash column chromatograph to afford the desired product **C**. LC/MS found: M+1=446.1

STEP C: [4-(5-Hydrazino-3-phenyl-[1,6]naphthyridin-2-yl)-benzyl]-carbamic acid *tert*-butyl ester (**D**)

To a solution of **C** (3.7g, 8.3mmol) in 22mL 1,4-dioxane was added hydrazine (6.1g, 189.1mmol) dropwise. The mixture was heated at 100°C in a microwave reactor for 5mins. Upon removal of the solvent, the residue was taken up in EtOAc and washed with saturated $NaHCO_3$ solution. The organic layer was washed by brine and dried over $MgSO_4$ and concentrated to afford the desired product **D**, which was used in the next step without further purification. LC/MS found: M+1=442.2

STEP D: [4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzyl]-carbamic acid *tert*-butyl ester (**E**)

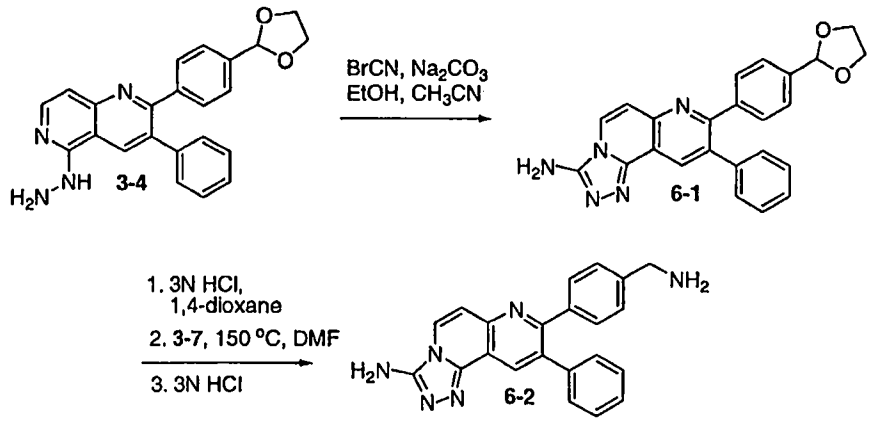
To a solution of **D** (3.8g, 8.6mmol) and *p*-toluenesulfonic acid monohydrate (0.08g, 0.4mmol) in 20mL toluene/methanol (3:1) was added trimethyl orthoacetate (1.4g, 11.6mmol). The solution was heated in microwave reactor at 100°C for 35mins. The reaction was quenched by $NaHCO_3$ (0.5g) solid. The organic layer was concentrated and purified on flash column chromatograph (100% EtOAc to10%MeOH/90%EtOAc over 35mins) to afford the desired product **E**.
LC/MS found: M+1=466.2

STEP E: 4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine (**5-3**)

To a solution of **E** (4.1g, 8.7mmol) in 80mL $CH_2Cl_2$ was added 40mL TFA dropwise. The mixture was stirred at room temperature for 15min. The solvent was removed. The residue was treated with $NaHCO_3$ (sat) until pH=9. The mixture was extracted with EtOAc (x6). The combined organic layers was concentrated and dried over $MgSO_4$. Upon removal of the solvent, the desired product **5-6** was obtained a yellow solid. LC/MS found: M+1=366.1

$^1$H-NMR ($CD_3OD$) δ 8.95 (s, 1 H), 8.66 (d, 1 H), 7.82 (d, 1 H), 7.60 (d, 2 H), 7.45 (d, 2 H), 7.42-7.34 (m, 5 H), 4.15 (s, 2H), 3.00 (s, 3 H).

SCHEME 6



8-[4-(Aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-2**)

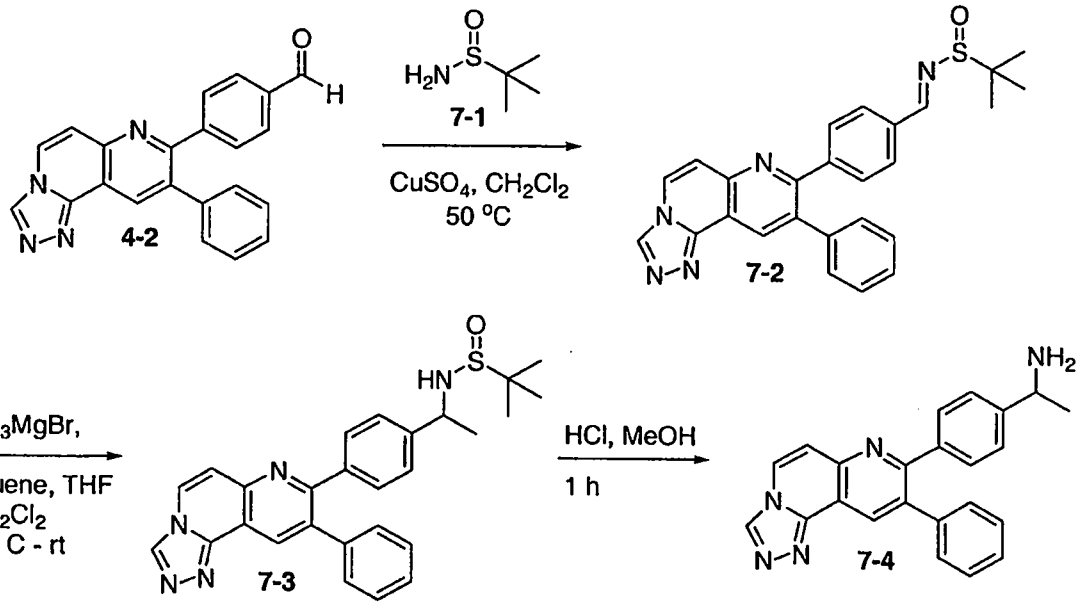
STEP A: 8-[4-(1,3-Dioxolan-2-yl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-1**)

To dry EtOH (1 mL) was added cyanogen bromide (0.104 mL, 0.52 mmol, 5M in MeCN) followed by sodium carbonate (96 mg, 0.91 mmol). [2-(4-[1,3]Dioxolan-2-yl-phenyl)-3-phenyl-[1,6]naphthyridin-5-yl]-hydrazine (**3-4**, 100 mg, 0.26 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was concentrated *in vacuo* and the resulting solid was used without further purification. LRMS m/z (M+1) Calcd: 410.2, found 410.1.

STEP B: 8-[4-(Aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-2**)

The title compound was prepared from 8-[4-(1,3-dioxolan-2-yl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine (**6-1**) using the procedures described in Scheme 5 (**5-1** to **5-3**). LRMS m/z (M+1) Calcd: 367.2, found 367.1.

SCHEME 7




1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl] ethanamine (**7-4**)

STEP A: 2-Methyl-N-{(1E)-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methylidene}propane-2-sulfinamide (**7-2**)

Racemic 2-methyl-2-propane-sulfinamide (**7-1**, 647 mg, 5.3 mmol), cupric sulfate (1.70g, 7.30mmol), and aldehyde **4-2** (511 mg, 1.45 mmol) were stirred in methylene chloride (10 mL) for 5d at 50°C. After cooling to rt, the mixture was filtered through celite, concentrated to a minimum volume and

purified via automated silica gel chromatography (0-10%MeOH in $CH_2Cl_2$ over 30 min) to give the title compound as a brown foam. LRMS m/z (M+1) Calcd: 454.2, found 454.2

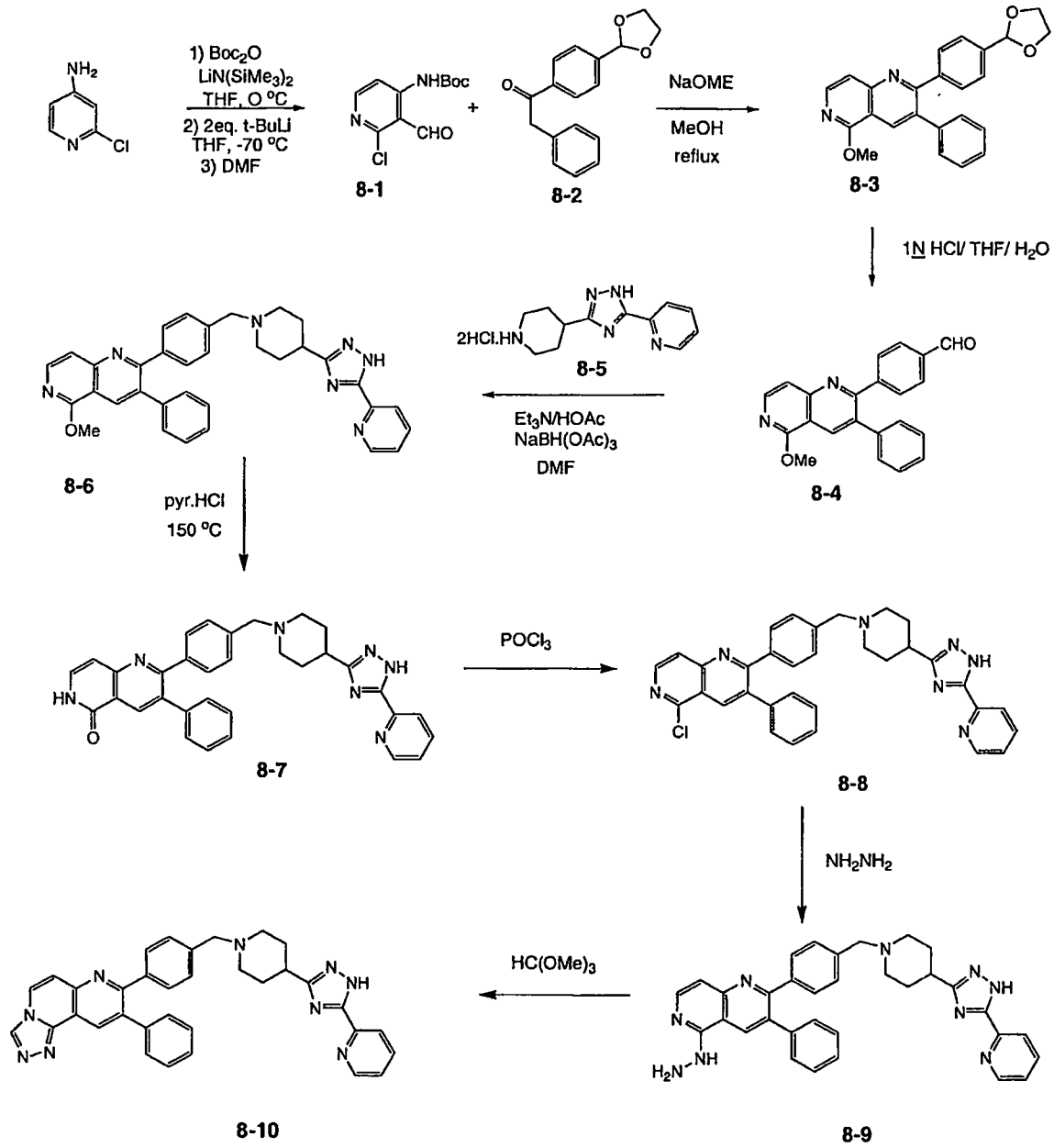
STEP B: 2-Methyl-N-{1-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethyl}propane-2-sulfinamide (7-3)

Methylmagnesium bromide solution (13.5 mL of 1.4 M solution in 3:1 toluene/THF, 19 mmol) was added to a stirred solution of 2-methyl-N-{(1E)-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methylidene}propane-2-sulfinamide (7-2, 298 mg, 0.66 mmol) in methylene chloride (5 mL) at -78°C and the solution was warmed to rt. After 18 h, the reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and concentrated to give an amber foam, which was purified via silica gel chromatography (0-10% MeOH/$CH_2Cl_2$ over 30min) to give the title compound as a yellow foam. LRMS m/z (M+1) Calcd: 470.2, found 470.3

STEP C: 1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl] ethanamine (7-4)

To a stirred solution of 2-methyl-N-{1-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethyl}propane-2-sulfinamide (7-3, 180 mg, 0.38 mmol) in methanol (6 mL) was added conc. HCl (1.5 mL ). After 1 h, water was added and the mixture was washed with methylene chloride. The aqueous portion was basified with saturated sodium carbonate solution and extracted with methylene chloride. 2N HCl (5 mL) was added to the organic layer and the mixture was concentrated to a minimum volume. The crude product was purified using reverse phase preparative HPLC to give the title compound as a pale yellow solid. LRMS m/z (M+1) Calcd: 366.2, found 366.3.

SCHEME 8




9-Phenyl-8-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridine (8-10)

tert-Butyl (2-chloro-3-formylpyridin-4-yl)carbamate (8-1)

A solution of 4-amino-2-chloropyridine (1.28 g, 10 mmol) and di-tert-butyl dicarbonate (2.21 g, 10.1 mmol) in THF (20 mL) was cooled to 0°C and a solution of 1M lithium bis(trimethylsilyl)amide in THF ( 20 mL, 20 mmol) was added slowly maintaining the temperature below 0°C. The reaction was allowed to warm to room temperature over one hour and then quenched by the addition of 1.5 N aqueous ammonium chloride (15 mL). The mixture was extracted into ethyl acetate,

washed with brine and the organic layer was dried ($Na_2SO_4$), filtered and evaporated. The residue was triturated with diethyl ether give pure tert-butyl (2-chloropyridin-4-yl)carbamate. The mother liquors were chromatographed on silica gel eluting with 25 – 45% ethyl acetate/ hexane to afford more product.

A solution of tert-butyl (2-chloropyridin-4-yl)carbamate (1.14 g, 5 mmol) in dry THF (20 mL) was cooled to -70°C under an inert atmosphere and 1.7 M t-butyl lithium/pentane (8 mL, 13.5 mmol) was slowly added. The reaction was stirred for two hours and then dry DMF (1.2 mL, 15.5 mmol) was added. The reaction was allowed to slowly warm to room temperature over a three hour period. The reaction mixture was quenched with 3 N HCl (12 mL) and diluted with diethyl ether. The ether layer was washed with aqueous $NaHCO_3$, dried (over $Na_2SO_4$), filtered and evaporated. The residue was triturated with cold diethyl ether to give pure t-butyl (2-chloro-3-formylpyridin-4-yl)carbamate. The mother liquors were chromatographed on silica gel eluting with 15-20% ethyl acetate/hexane to give additional product. 1H-NMR(500 MHz, $CDCl_3$): δ 11.0 (1H, br s), 10.52 (1H, s), 8.38 (1H, d, J= 6 Hz), 8.31 (1H, d, J= 6 Hz), 1.54 (9H, s); m/e (m+1): 257.2.

1-[4-(1,3-Dioxolan-2-yl)phenyl]-2-phenylethanone (8-2)

To a solution of 4-cyanobenzaldehyde (20.0 g, 152.5 mmol) and ethylene glycol (25.5 mL, 457.5 mmol) in toluene (250 mL) was added p-toluenesulfonic acid (300 mg). The flask was equipped with a Dean-Stark trap and the mixture heated to reflux. After 5 hr the mixture was concentrated. The residue was taken up in ethyl acetate and washed with saturated $NaHCO_3$, water (2x), and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give 4-(1,3-dioxolan-2-yl)benzonitrile as a clear oil which solidified under vacuum: 1H-NMR (500 MHz, $CDCl_3$): δ 7.67 (2 H, d, J = 8.06 Hz), 7.59 (2 H, d, J = 8.30 Hz), 5.85 (1H, s), 4.13-4.05 (4H, m).

To a solution of 4-(1,3-dioxolan-2-yl)benzonitrile (5.0 g, 28.54 mmol) in anhydrous THF (100 mL) was added benzyl magnesium chloride (36 mL, 20% wt solution in THF, 43 mmol) slowly at 0°C. After one hour the mixture was warmed to room temperature. After four hours the mixture was cooled to 0°C and quenched with saturated $NH_4Cl$. The mixture was warmed to room temperature and extracted with ethyl acetate (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography(10% ethyl acetate/hexanes) gave 1-[4-(1,3-dioxolan-2-yl)phenyl]-2-phenylethanone as a pale yellow solid: 1H-NMR (500 MHz, $CDCl_3$): δ 8.02 (2 H, d, J = 8.30 Hz,), 7.57 (2 H, d, J = 8.30 Hz,), 7.38-7.24 (5H, m), 5.86 (1H, s), 4.29 (2H, s), 4.28-4.09 (4H, m).

2-[4-(1,3-Dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine (8-3)

To a partial solution of 1-[4-(1,3-dioxolan-2-yl)phenyl]-2-phenylethanone (997 mg, 3.72 mmol) and tert-butyl (2-chloro-3-formylpyridinn-4-yl)carbamate (924 mg, 3.6 mmol) in dry methanol (14 mL) was added 25 wt % sodium methoxide/methanol (2.5 mL, 11.4 mmol). The reaction mixture was warmed at 65°C for four hours. The cooled reaction was concentrated to remove the methanol and the residue was partitioned between water and ethyl acetate. The organic layer was dried ($Na_2SO_4$), filtered and evaporated. The residue was triturated with cold ether to give pure 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine. The mother liquors were purified by chromatography on silica

gel and elution with 20-40% ethyl acetate/hexane gave additional product. 1H-NMR (500 MHz, $CDCl_3$): δ 8.54 (1H, s), 8.23 (1H, d, J=5.9 Hz), 7.55 (1H, d, J= 5.9 Hz), 7.48 (2H, d, J= 8 Hz), 7.40 (2H, d, J=8 Hz), 7.29-7.30 (3H, m), 7.22-7.25 (2H, m), 4.16 (3H, s), 4.02-411 (4H, 2 m). m/e (m+1): 385.1.

4-(5-Methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzaldehyde (8-4)

To a solution of 2-[4-(1,3-dioxolan-2-yl)phenyl]-5-methoxy-3-phenyl-1,6-naphthyridine (760 mg, 1.98 mmol) in THF (8 mL) was added 1 N HCl (6 mL) and the solution was stirred for three hours. Ethyl acetate was added and the mixture was made basic with aqueous $Na_2CO_3$. The organic layer was dried ($Na_2SO_4$), filtered and the solvent evaporated. The residue was triturated with diethyl ether to give pure product. The mother liquors were purified by column chromatography on silica gel and elution with 10-30% ethyl acetate/hexane gave additional product. 1H-NMR (500 MHz, $CDCl_3$): δ 10.10 (1H, s), 8.60 (1H, s), 8.26 (1H, d, J= 6Hz), 7.81 (2H, d, J=8.3Hz), 7.62 (2H, d, J=8.3Hz), 7.56 (1H, d, J=6.1Hz), 7.30-7.32 (3H, m), 7.21-7.23 (2H, m), 4.17 (3H, s). m/e (m+1): 341.1.

2-(3-Piperidin-4-yl-1H-1,2,4-triazol-5-yl)pyridine Dihydrochloride (8-5)

Carbonyl diimidazole (3.57 g, 22 mmol) was added to a solution of 1-(tert-butoxycarbonyl)-piperidine-4-carboxylic acid (4.59 g, 20 mmol) in methylene chloride (50 mL) and stirred for two hours until gas evolution ceased. Then hydrazine (0.8 mL, ~26 mmol) was added to the reaction and the reaction was stirred at room temperature for another two hours. The reaction was diluted with more methylene chloride and washed with sat'd aqueous $NaHCO_3$. The organic layer was dried over anhydrous $Na_2SO_4$, filtered and the solvent evaporated to give a viscous residue. Trituration with diethyl ether afforded tert-butyl 4-(hydrazinocarbonyl)-piperidine-1-carboxylate as an off-white solid. 1H NMR(500 MHz, $CDCl_3$): δ 6.77 (1H, br s), 4.15 (2H, br s), 3.90 (2H, v br s),2.75 (2H, b s), 2.22 (1H, m), 1.78 (2H, br d, J=11.9 Hz), 1.66 (2H, br q, J=12.2 Hz, J=27.5 Hz), 1.47 (9H, s).

This material (2.43g, 10 mmol) was dissolved in anhydrous 2-ethoxyethanol (20 mL) and 2-cyanopyridine (1.14 g, 11 mmol) was added to the solution. After 25 wt. % sodium methoxide/methanol (1.1 mL, ~5 mmol) was added the mixture was heated to 130°C for 16 hours. The cooled reaction was neutralized with acetic acid and partitioned between ethyl acetate and aq. $NaHCO_3$. The organic layer was dried over $Na_2SO_4$, the salts removed by filtration and the solvent evaporated under vacuum. This residue was triturated with diethyl ether to give tert-butyl 4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate as a white solid. 1H NMR(500 MHz, $CDCl_3$): δ 8.70 (1H, d, J= 3.9Hz), 8.19 (1H, d, J=7.9Hz), 7.87 (1H, d t, J=1.7Hz, J=8Hz), 7.40 (1H, m), 4.20 (2H, br s), 3.03 (1H, m), 2.95 (2H, br s), 2.09 (2H, br d, J=12 Hz), 1.86 (2H, br q, J= 4.2Hz), 1.49 (9H, s); m/e (m+1): 330.2

This material (2.68 g, 8.14 mmol) was suspended in 4 N HCl/dioxane. The stoppered reaction mixture was stirred at room temperature for 16 hours and then diluted with diethyl ether. The solids were isolated by filtration and the hygroscopic solid was digested in acetonitrile. This solid was isolated by filtration and partially dissolved in hot methanol. Upon cooling and addition of some ethyl ether to the solution 2-(3-piperidin-4-yl-1H-1,2,4-triazol-5-yl)pyridine slowly precipitated as the

dihydrochloride salt. 1H NMR (500 MHz, DMSO-d6): δ 9.10 (1H, br s), 8.92 (1H, br s), 8.73 (1H, d, J=4.9Hz), 8.10-8.20 (2H, m), 7.64 (1H, t, J=5.7 Hz), 3.33 (2H, br d, J=12.7 Hz), 3.16 (1H, m), 3.05 (2H, br q, J=11.9 Hz, J=21.8 Hz),2.18 (2H, br d, J=11.5 Hz), 1.99 (2H, br q, j=11.0 Hz, J=22.2 Hz): m/e(m+1): 230.3.

5-Methoxy-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperdin-1-yl] methyl}phenyl-1,6-naphthyridine (**8-6**)

To a solution of 2-(3-piperidin-4-yl-1H-1,2,4-triazol-5-yl)pyridine dihydrochloride (542 mg, 1.80 mmol) and 4-(5-methoxy-3-phenyl-1,6-naphthyridin-2-yl)benzaldehyde (560 mg, 1.65 mmol) in dry DMF (6 mL) was added triethylamine ( 0.83 mL, 6 mmol). After stirring for 10 minutes, acetic acid (1.03 mL, 18 mmol) was added and the mixture was stirred at room temperature over night. Then sodium triacetoxy borohydride (367 mg, 1.73 mmol) was added in one portion and stirred for six hours. After monitoring by LC/MS determined the reaction was not complete, additional portions of sodium triacetoxy borohydride (2 x 90 mg) were added over the next several hours at which time the reaction was complete. The mixture was diluted with ethyl acetate and aqueous $Na_2CO_3$ was added. The organic layer was separated and washed twice with water, dried ($Na_2SO_4$) and the solvent evaporated. The residue was digested with acetonitrile and upon cooling the solid product was isolated by filtration. This solid was suspended in hot ethyl acetate and methanol was slowly added until there was complete dissolution. The solvents were then boiled down to a small volume and allowed to cool as the pure product crystallized out. The mother liquors were purified by column chromatography on silica gel and elution with 1- 7% methanol/ethyl acetate gave additional product. 1H NMR(500 MHz, $CDCl_3$): δ 8.66 (1H, d, J= 4.7Hz), 8.54 (1H, s), 8.23 (1H, d, J=6 Hz), 8.16 (1H, d, J=7.8Hz), 7.83 (1H, dt, J= 1.7Hz, J=7.8 Hz), 7.56 (1H, d, J=6 Hz), 7.40 (2H, d, J= 8Hz), 7.36 (1H, dd), 7.28-7.30 (3H, m), 7.23-7.25 (2H, m), 4.16 (3H, s), 3.54 (2H, s), 2.96 (2H, br d, J= 11.5Hz), 2.85 (1H, t, J=3.7Hz), 2.06-2.17 (4H, m), 1.92-2.01(2H, m). m/e(m+1): 554.3, 277.9 [(m+2)/2].

3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridin-5(6H)-one (**8-7**)

A mixture of 5-methoxy-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperdin-1-yl] methyl}phenyl)-1,6-naphthyridine (725 mg, 1.31 mmol) and pyridine hydrochloride (6.9 gm, ~60 mmol) was heated at 150°C for ten minutes. The cooled residue was dissolved in the minimum amount of water and neutralized with aqueous $NaHCO_3$. The precipitated solid was collected by filtration and purified by column chromatography on silica gel eluting with 1-14% methanol/ethyl acetate (sat'd $NH_4OH$). The isolated product was digested in methanol/acetonitrile to give pure product. 1H NMR(500 MHz, DMSO-d6): δ 11.58 (1H, d, J=4.8Hz), 8.68 (1H, br s), 8.39 (1H, s), 8.03 (1H, d, J=7.3Hz), 7.50 (2H, t, J=6.5Hz), 7.31-7-33 (5H, m), 7.24-7.25 (4H, m), 6.79 (2H, d, J=7.3Hz), 3.50 (2H, s), 2.84 (2H, br d, J=10.5Hz), 2.72 (1H, m), 2.08 (2H, br t, J=11 Hz), 1.95 (2H, br d, J=11.6Hz), 1.77 (2H, m). m/e(m+1): 540.3, 270.9 [(m+2)/2].

5-Chloro-3-phenyl-2-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,6]naphthyridine (**8-8**)

A mixture of **8-7** (5.5g, 10.2mmol) and $POCl_3$ (50.0g, 326.1mmol) and DMF (0.3g, 4.1mmol) was heated to reflux at 130°C for 3hr. The reaction mixture was cooled and concentrated to remove $POCl_3$. 40mL Toluene was added and concentrated to obtain a solid. To the solid was added 50mL $H_2O$ and 40mL $NaHCO_3$ (saturated) and 20mL 1NNaOH to pH=9. The mixture was stirred to precipitate a solid which was collected via filtration as the desired product **8-8**. It was washed by water and $CH_3CN$ and dried under vacuum.

LC/MS: M+1=559.09

(3-Phenyl-2-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,6]naphthyridin-5-yl)-hydrazine (**8-9**)

A suspension of **8-8** (4.3g, 7.7mmol) in 30mL 1,4-dioxane and hydrazine (7.4g, 231.1mmol) was heated in a microwave reactor at 100°C for 5mins. The mixture was cooled and concentrated to remove solvents. Toluene 40mL (x3) was added and removed under vacuum to remove the residual hydrazine. The desired product **8-9** was obtained as a solid.

LC/MS: M+1=554.4

9-Phenyl-8-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridine (**8-10**)

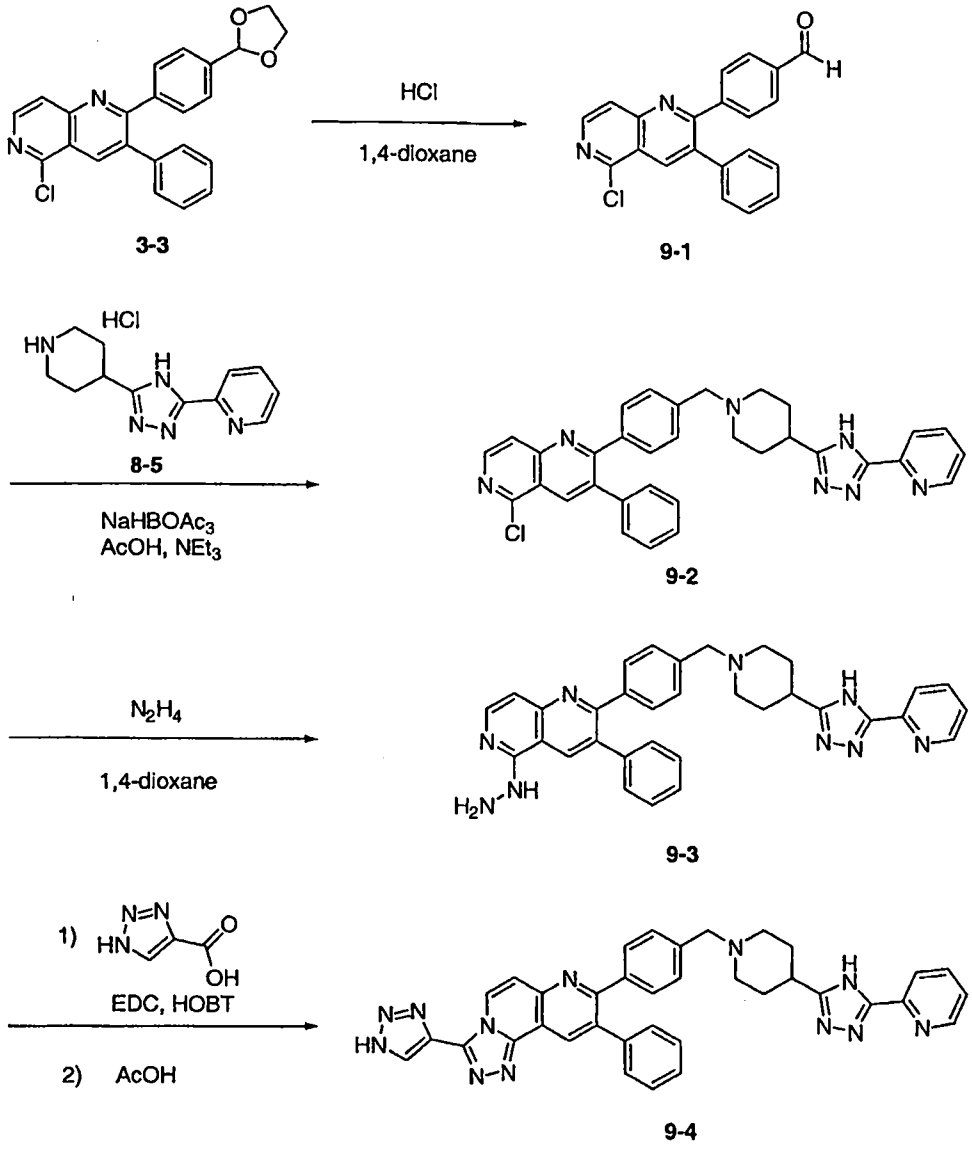
To a solution of **8-9** (4.5g, 8.1mmol) in 20mL methanol and 60mL toluene was added trimethoxy orthoformate (3.5g, 32.5mmol) and toluenesulfonic acid (0.1g, 0.8mmol). The mixture was refluxed for 10 hrs. Upon removal of the solvent, the residue was purified by flash column chromatography (100% $CHCl_3$ to 50%$CHCl_3$ and 50% methanol) to afford the desired product **8-10**.

HRMS: M+1 (cal) =564.2619; found = 564.2589

1H NMR(500 MHz, $CD_3OD$): δ 9.35 (1H, s), 8.96 (1H, s), 8.72 (1H, d), 8.59 (1H, d), 8.28-8.10 (2H, m), 7.68-7.48 (6H, m), 7.40-7.30 (5H, m), 4.40 (2H, s), 3.68-3.20 (5H, m), 2.50-2.10 (4H, m).

80

SCHEME 9




9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (9-4)

4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzaldehyde (9-1)

To a stirred solution of **3-3** (16g, 41.1mMol) in anhydrous 1,4-dioxane (75mL) at 0°C was added 3N HCl (27mL). The reaction was then allowed to reach room temperature and was stirred for around 3 hours. Upon completion, the reaction was quenched with saturated $NaHCO_3$ solution to reach a pH of >7. The product was extracted into ethyl acetate (3 x 150mL). The combined organic layers were washed with brine, dried with $Na_2SO_4$ and $MgSO_4$, filtered and concentrated *in vacuo* to yield 4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzaldehyde **9-1** as a tan solid. LC/MS (M+1) calculated: 345.8; observed: 345.0

5-chloro-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (**9-2**)

To a stirred solution of **9-1** (4.9g, 14.2mMol) and **8-5** (4.2g, 15.6mMol) in NMP (50mL) was added triethylamine (6mL, 42.6mMol) followed by acetic acid (1.6mL, 28.4mMol). After stirring at ambient temperature overnight, sodium triacetoxyborohydride (3.6g, 17mMol) was added in portions. Upon completion, the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, followed by water, then brine. The organic layer was dried with $Na_2SO_4$ and $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue purified using flash chromatography on silica (gradient: 0% to 10% MeOH in $CHCl_3$ over 25min) to yield **9-2** as an orange solid. LC/MS (M+1) calculated: 559.1; observed: 559.2

5-hydrazino-3-phenyl-2-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (**9-3**)

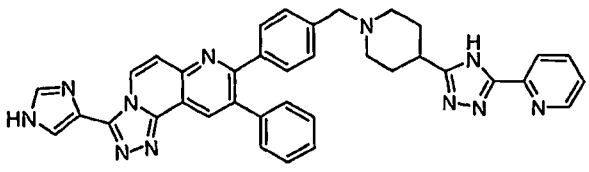
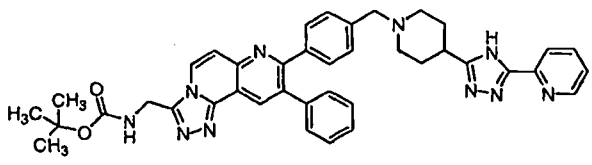
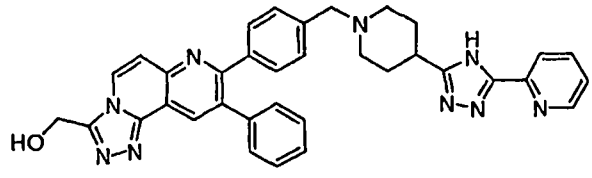
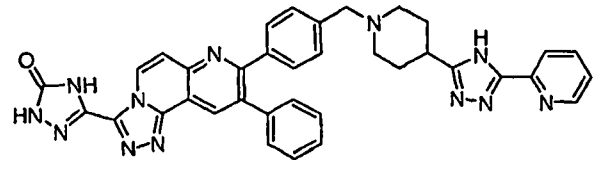
To a stirred solution of **9-2** (5g, 8.9mMol) in anhydrous 1,4-dioxane (20mL) was added hydrazine (5.9mL, 188.1mMol). The solution was heated to 100°C in a microwave reactor for 5 minutes. The solvent was removed *in vacuo* and was dried azeotropically with toluene three times. The crude solid was triturated with a saturated $NaHCO_3$ solution for 20 minutes. The suspension was filtered and washed with copious amounts of water. The solid was dried azeotropically with toluene three times to yield **9-3** as a tan solid. LC/MS (M+1) calculated: 554.6; observed: 554.2

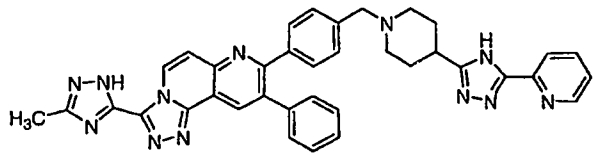
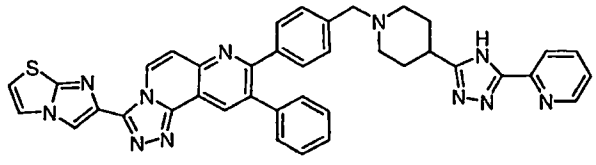
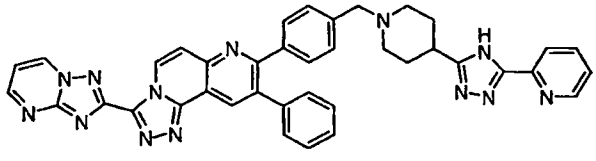
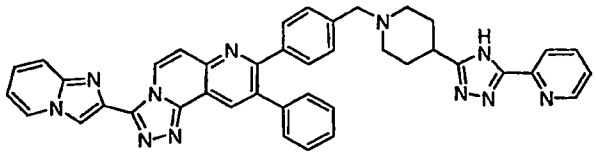
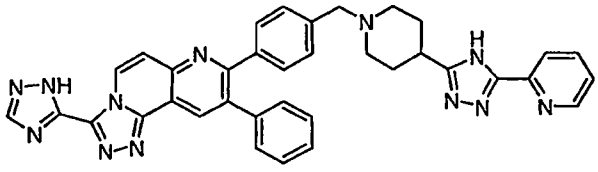
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**9-4**)

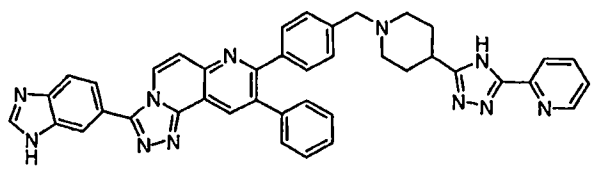
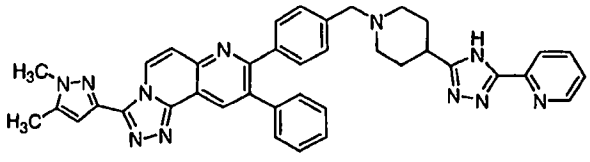
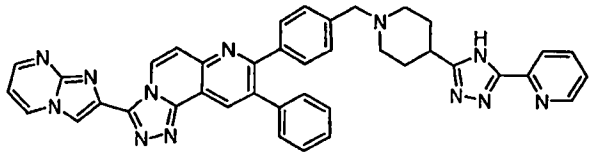
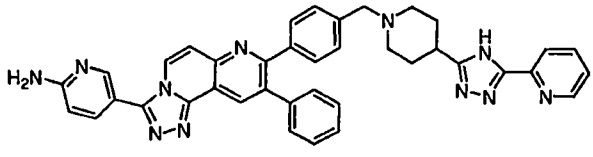
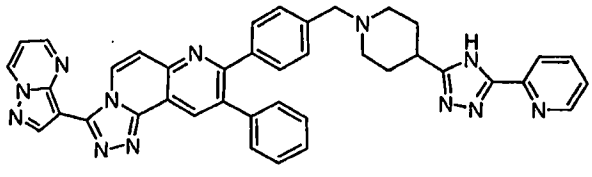
To a stirred solution of **9-3** (2.0g, 3.6mMol), HOBT (0.5g, 3.9mMol), and 1H-1,2,3-triazole-4-carboxylic acid (0.4g, 3.9mMol) in anhydrous DMF (20mL) was added DIEA (1.2mL, 7.2mMol) followed by EDC (0.76g, 3.9mMol). The solution was stirred at ambient temperature overnight. The solution was then treated with 2mL of acetic acid and was heated to 80°C for 3hrs. Upon cooling to room temperature, the solution was filtered through a syringe filter and purified on a C18 reverse phase HPLC to give **9-4** as a solid. Mass (M+1) calculated: 631.2789 observed: 631.2778

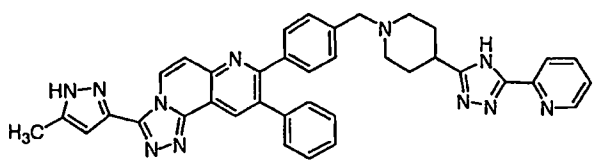
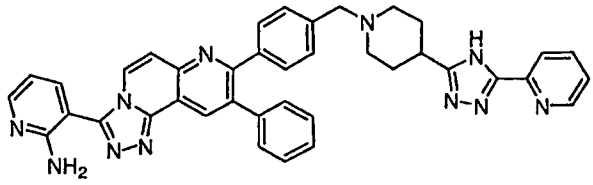
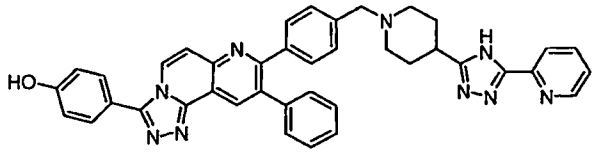
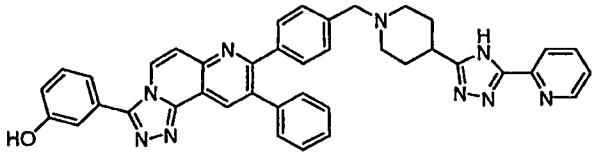
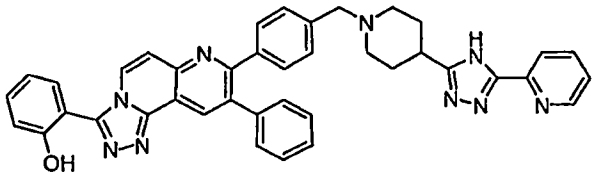
The following table (Table 3) contains compounds made using the procedures of Scheme 9, substituting the appropriate amine for **8-9** and the appropriate carboxylic acid for 1H-1,2,3-triazole-4-carboxylic acid. Compounds **9-5** – **9-8** and **9-13** – **9-25** were isolated as HCl salts. Compounds **9-9** – **9-12** were isolated as TFA salts.

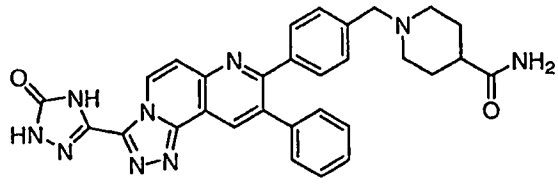
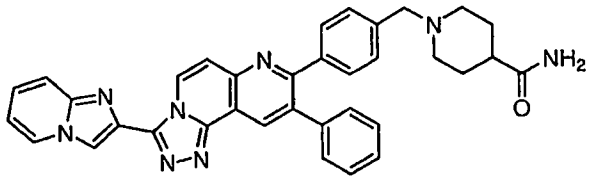
Table 3

| Cmp | Structure | Name | LRMS m/z (M+H) |
|---|---|---|---|
| **9-5** |  | 3-(1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 630.2831 |
| **9-6** |  | tert-butyl [9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-yl]methylcarbamate | 693.3394 |
| **9-7** |  | [9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol | 594.2703 |
| **9-8** |  | 5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]-2,4-dihydro-3H-1,2,4-triazol-3-one | 647.2729 |

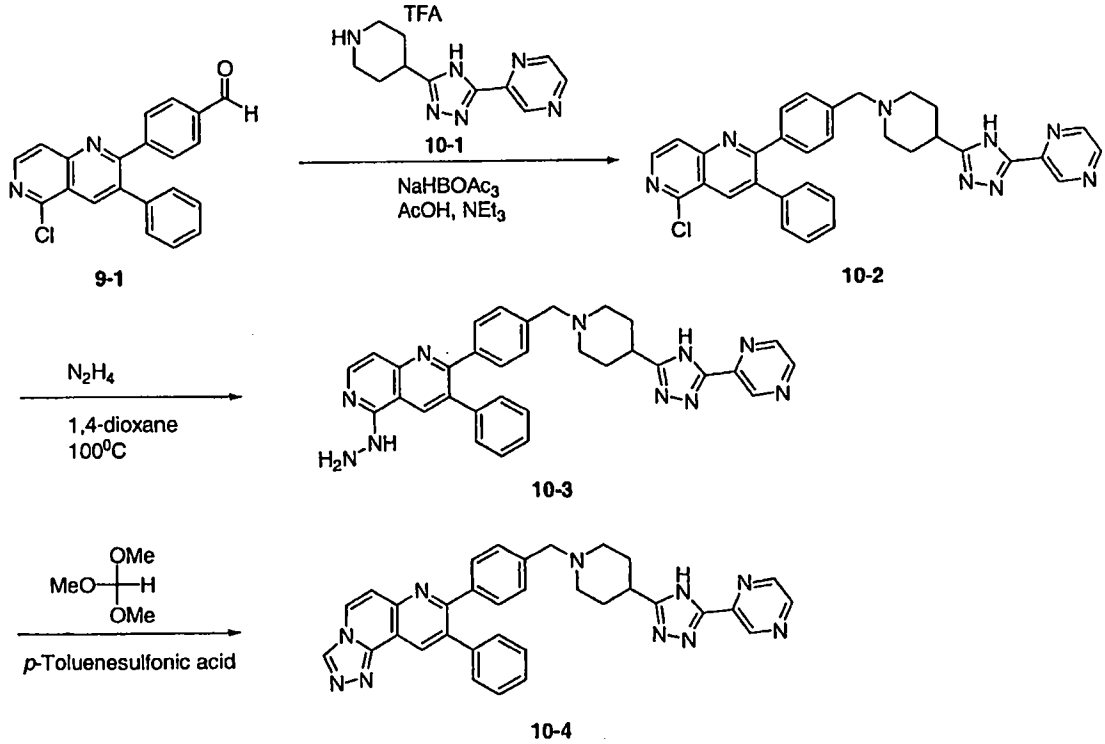
| | | | |
|---|---|---|---|
| 9-9 |  | 3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 645.2948 |
| 9-10 |  | 3-imidazo[2,1-b][1,3] thiazol-6-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 686.2547 |
| 9-11 |  | 9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4] triazolo[3,4-f]-1,6-naphthyridine | 682.2902 |
| 9-12 |  | 3-imidazo[1,2-a]pyridin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | LRMS (M+1)= 680.3 |
| 9-13 |  | 9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,4-triazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 631.2792 |

| | | | |
|---|---|---|---|
| 9-14 |  | 3-(1H-benzimidazol-6-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 680.2988 |
| 9-15 |  | 3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 658.3145 |
| 9-16 |  | 3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 681.2949 |
| 9-17 |  | 5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine | 656.2988 |
| 9-18 |  | 9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 681.2951 |

| | | | |
|---|---|---|---|
| 9-19 |  | 3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 644.2998 |
| 9-20 |  | 3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine | 656.298 |
| 9-21 |  | 4-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol | 656.288 |
| 9-22 |  | 3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol | 656.288 |
| 9-23 |  | 2-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol | 656.2894 |

| | | | |
|---|---|---|---|
| 9-24 |  | 1-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide | 546.2344 |
| 9-25 |  | 1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]piperidine-4-carboxamide | 579.2598 |

SCHEME 10




9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**10-4**)

2-(3-piperidin-4-yl-1*H*-1,2,4-triazol-5-yl)pyrazine (**10-1**)

To a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (120 g, 520 mmol) in DCM (250 mL) was added carbonyldiimidazole (96 g, 590 mmol) in portions at room temperature. After 30 minutes, the reaction mixture was added to a freshly prepared solution of hydrazine (27 g, 840 mmol) in DCM (100 mL). After 30 minutes, the reaction was washed with a saturated solution of sodium carbonate, brine, dried over sodium sulfate, filtered and concentrated. The resulting solid was suspended in ether and filtered to give *tert*-butyl 4-(hydrazinocarbonyl)piperidine-1-carboxylate as a white solid. $^1$H NMR (400 MHz, DMSO –$d_6$): δ 9.00 (s, 1H), 4.15-4.10 (s, 2H), 3.95-3.90 (m, 2H), 2.80-2.60 (m, 2H), 2.25-2.20 (m, 1H), 1.62-1.55 (m, 2H), 1.40 (s, 9H).

A solution of pyrazinecarbonitrile (2.0 g, 19 mmol) in methanol (20 mL) was treated with sodium methoxide in methanol (25wt%, 1.3 mL, 5.7 mmol) at room temperature. After 30 minutes, a solution of *tert*-butyl 4-(hydrazinocarbonyl)piperidine-1-carboxylate (4.6 g, 19 mmol) in methanol (20 mL) was added and the reaction was heated to reflux for 19 hours. The reaction mixture was concentrated, dissolved in ethoxyethanol (50 mL) and heated to reflux for 22 hours. The reaction was cooled to room temperature, quenched with acetic acid (0.38 mL, 6.6 mmol) and concentrated. The residue was suspended in ether and filtered to give *tert*-butyl 4-(5-pyrazin-2-yl-1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate as a solid. HRMS ($M+H^+$): observed = 331.1876, calculated = 331.1877; $^1$H NMR (400 MHz, $CD_3OD$): δ 9.29 (d, J = 1.6 Hz, 1H), 8.70 (dd, J = 2.4, 1.6 Hz, 1H), 8.64 (d, J = 2.4 Hz, 2H), 4.19-4.15 (m, 2H), 3.15-3.09 (m, 1H), 2.97 (m, 2H), 2.07-2.03 (m, 2H), 1.84-1.75 (m, 2H), 1.48 (s, 9H).

A solution of *tert*-butyl 4-(5-pyrazin-2-yl-1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate (6.0 g, 18 mmol) in trifluoroacetic acid (25 mL) was stirred at room temperature. After 1 hour, the reaction was concentrated. The resulting solid was suspended in ethyl acetate and methanol and filtered to give **10-1** as the TFA salt. The salt was dissolved in 1:1 acetonitrile:water, loaded onto an SCX ion exchange resin, rinsed with acetonitrile, and eluted with 10% NH3 in ethanol to give **10-1** as a solid. $^1$H NMR (400 MHz, $CDCl_3$): δ 9.28-9.26 (m, 1H), 8.70-8.68 (m, 1H), 8.60-8.58 (m, 1H), 3.35-3.22 (m, 2H), 3.15-3.05 (m, 1H), 2.90-2.85 (m, 2H), 2.15-2.08 (m, 2H), 1.95-1.90 (m, 2H).

5-chloro-3-phenyl-2-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (**10-2**)

To a stirred solution of **9-1** (1g, 2.9mMol) and **10-1** (1.09g, 3.2mMol) in NMP (10mL) was added triethylamine (0.8mLmL, 5.8mMol) followed by acetic acid (0.3mL, 5.8mMol). After stirring at ambient temperature overnight, sodium triacetoxyborohydride (0.6g, 2.9mMol) was added in portions. Upon completion, the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, followed by water, then brine. The organic layer was dried with $Na_2SO_4$ and $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified using flash chromatography on silica (gradient: 0% to 10% MeOH in $CHCl_3$ over 25min) to yield **10-2** as a solid. LC/MS (M+1) calculated: 560.1; observed: 560.2

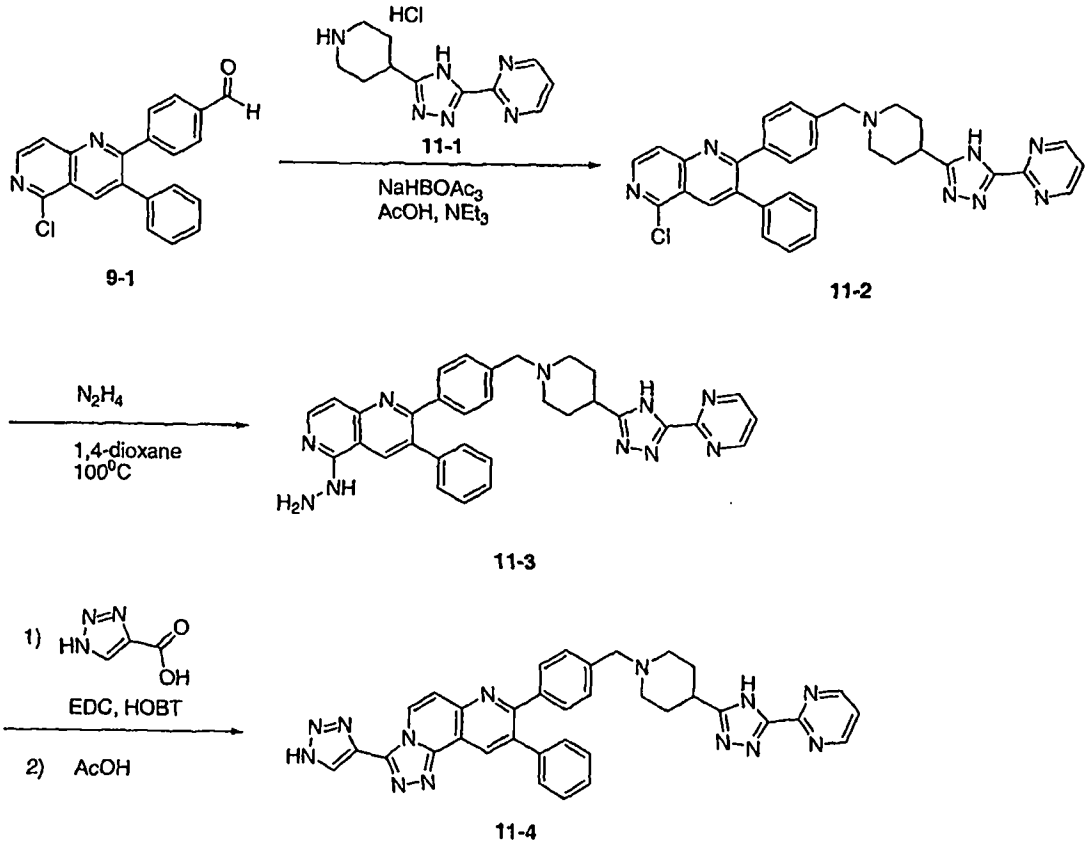
5-hydrazino-3-phenyl-2-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (**10-3**)

To a stirred solution of **10-2** (0.5g, 0.9mMol) in anhydrous 1,4-dioxane (5mL) was added hydrazine (0.56mL, 17.8mMol). The solution was heated to 100°C in a microwave reactor for 20 minutes. The solvent was removed *in vacuo* and was dried azeotropically with toluene three times. The crude solid was triturated with a saturated $NaHCO_3$ solution for 20 minutes. The suspension was filtered and washed with copious amounts of water. The solid was dried azeotropically with toluene three times to yield **10-3** as a brown solid. *LC/MS* (M+1) calculated: 555.6; observed: 555.2

9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**10-4**)

To a stirred solution of **10-3** (0.5g, 0.9mMol) in 16mL of 3:1 toluene:methanol was added trimethyl orthoformate (0.3g, 2.7mMol) and *p*-toluenesulfonic acid monohydrate (0.017g, 0.09mMol). The reaction was heated to 100°C in a microwave reactor for 1 hour. After cooling to room temperature, the solvent was removed under reduced pressure. The product was purified on a C18 reverse phase HPLC to give **10-4** as a solid. Mass (M+1) calculated: 565.2571 observed: 565.2523

SCHEME 11



9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl} phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (11-4)

2-(3-piperidin-4-yl-1*H*-1,2,4-triazol-5-yl)pyrimidine (11-1)

A mixture of *tert*-butyl 4-(hydrazinocarbonyl)piperidine-1-carboxylate (10.1 g, 41.5 mmol) and 2-cyanopyrimidine (4.36 g, 41.5 mmol) in 1-butanol (20 mL) was heated to reflux for 48 hours. The mixture was concentrated, suspended in ether, and filtered to give *tert*-butyl 4-(5-pyrimidin-2-yl-1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate as a solid. MS ($M+H^+$): 331.2 observed; $^1$H-NMR (400 MHz, $CD_3OD$): δ 8.92 (d, J=4.0Hz, 2H), 7.52 (t, J=4.0Hz, 1H), 4.18-4.15 (m, 2H), 3.14-3.08 (m, 1H), 2.98 (br.s, 2H), 2.07-2.01 (m, 2H), 1.85-1.77 (m, 2H), 1.48 (s, 9H).

To a solution of *tert*-butyl 4-(5-pyrimidin-2-yl-1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate (13.6 g, 41.1 mmol) in methanol (30 mL) and DCM (15 mL) was added a saturated solution of anhydrous HCl in ethyl acetate (60 mL). After 2 hours, the reaction was concentrated. The resulting solid was suspended in ethyl acetate and methanol and filtered to give **11-1** as the HCl salt. The salt was dissolved in 1:1 acetonitrile:water, loaded onto an SCX ion exchange resin, rinsed with acetonitrile, and eluted with 10% $NH_3$ in ethanol to give **11-1** as a solid. MS ($M+H^+$): 231.2

5-chloro-3-phenyl-2-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (11-2)

To a stirred solution of **9-1** (0.25g, 0.73mMol) and **11-1** (0.23g, 0.87mMol) in NMP (5mL) was added triethylamine (0.3mL, 2.2mMol) followed by acetic acid (0.082mL, 1.5mMol). After stirring at ambient temperature overnight, sodium triacetoxyborohydride (0.18g, 0.87mMol) was added. Upon completion, the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, followed by water, then brine. The organic layer was dried with $Na_2SO_4$ and $MgSO_4$, filtered and concentrated *in vacuo* to yield **11-2**. LC/MS calculated: 559.1; observed: 559.3

5-hydrazino-3-phenyl-2-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (11-3)

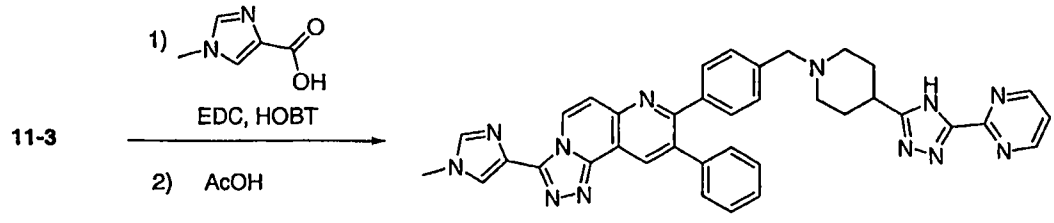
To a stirred solution of **11-2** (0.4g, 0.7mMol) in anhydrous 1,4-dioxane (3mL) was added hydrazine (0.45mL, 14.5mMol). The solution was heated to 100°C in a microwave reactor for 5 minutes. The solvent was removed *in vacuo* and was dried azeotropically with toluene three times to yield **11-3**. LC/MS (M+1) calculated: 555.6; observed: 555.4

9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl} phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (11-4)

To a stirred solution of **11-3** (0.2g, 0.36mMol), HOBT (0.05g, 0.4mMol), and 1H-1,2,3-triazole-4-carboxylic acid (0.05g, 0.4mMol) in anhydrous DMF (2mL) was added DIEA (0.18mL, 1.1mMol) followed by EDC (0.08g, 0.4mMol). The solution was heated in the microwave reactor for 30 minutes at 80°C. Solution was then treated with 0.5mL of acetic acid and was heated to 80°C in the microwave reactor for 10min. Upon cooling to room temperature, the solution was passed through a

syringe filter and purified on a C18 reverse phase HPLC to give **11-4** as a solid. Mass (M+1) calculated: 632.2742 observed: 632.274

SCHEME 12

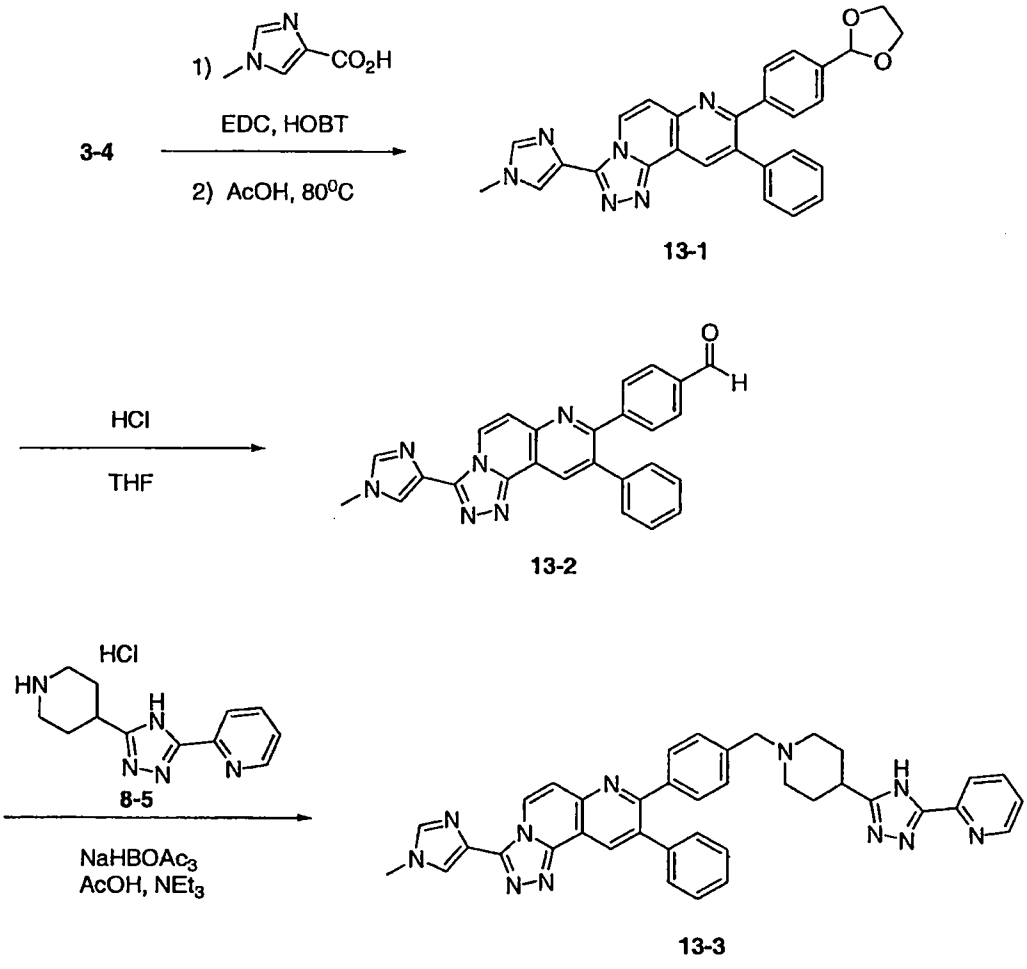



**12-1**

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**12-1**)

To a stirred solution of **11-3** (0.23g, 0.4mMol), HOBT (0.06g, 0.45mMol), and 1-methyl-1H-imidazole-4-carboxylic acid (0.06g, 0.45mMol) in anhydrous DMF (2mL) was added DIEA (0.13mL, 0.8mMol) followed by EDC (0.09g, 0.5mMol). The solution was heated in the microwave reactor for 15 minutes at 80°C. Solution was then treated with 0.2mL of acetic acid and was heated to 80°C in the microwave reactor for 20 minutes. Upon cooling to room temperature, the solution was passed through a syringe filter and purified on a C18 reverse phase HPLC to give **12-1** as a solid. Mass (M+1) calculated: 632.2742 observed: 632.274

SCHEME 13




3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-3**)

8-[4-(1,3-dioxolan-2-yl)phenyl]-3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-1**)

To a stirred solution of **3-4** (5g, 13mMol), HOBT (1.9g, 14.3mMol), and 1-methyl-1H-imidazole-4-carboxylic acid (2g, 15.6mMol) in anhydrous DMF (100mL) was added EDC (2.7g, 14.3mMol). The solution was stirred overnight at ambient temperature. The solution was then treated with 24mL of acetic acid and was heated to 80°C in an oil bath for 5 hours. Upon cooling to room temperature, an equal volume of water was added and the resulting suspension was filtered and washed with copious amounts of water. The collected solid was dried azeotropically with toluene three times to yield **13-1** as a tan solid. Mass (M+1) calculated: 475.1877 observed: 475.1871

4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzaldehyde (**13-2**)

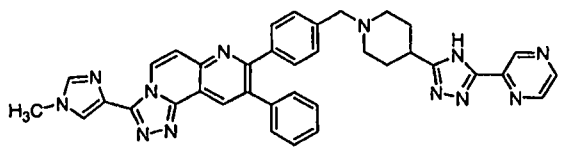
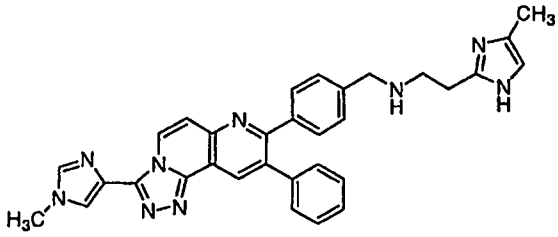
To a stirred solution of **13-1** (2g, 4.2mMol) in THF (32mL) was added 1N HCl (32mL). A suspension developed as the reaction stirred at room temperature for 1 hour. The reaction was then quenched with 100mL of a saturated $NaHCO_3$ solution. The suspension was filtered and washed with water. The collected solid was dried azeotropically with toluene three times to yield **13-2** as a tan solid. Mass (M+1) calculated: 431.1615 observed: 431.1616

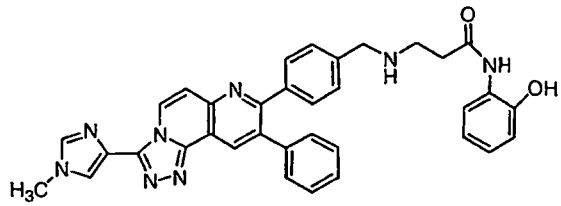
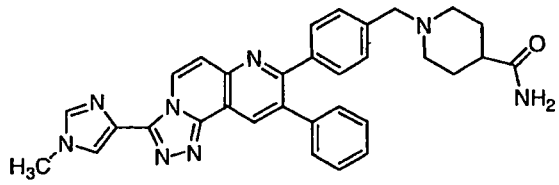
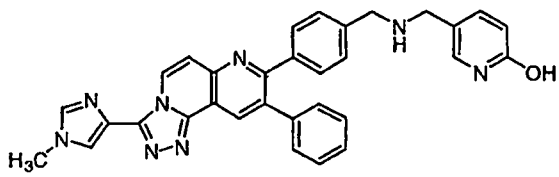
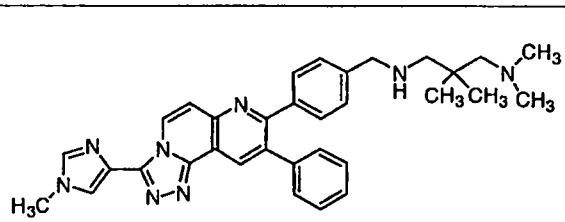
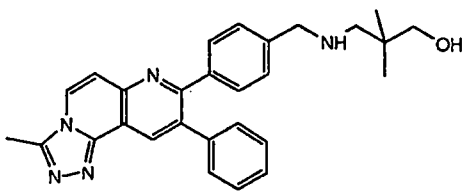
3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-3**)

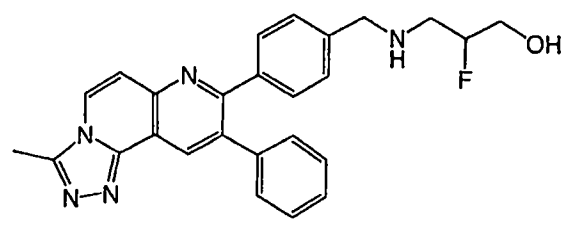
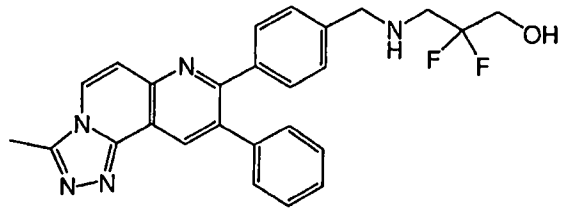
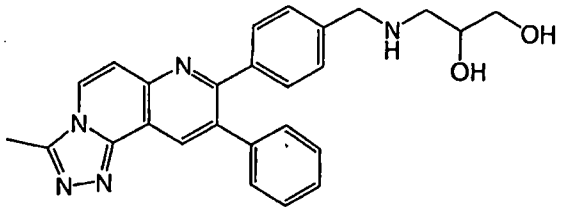
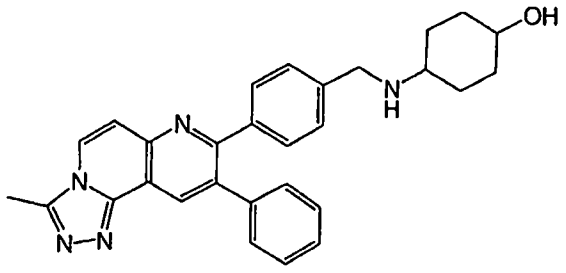
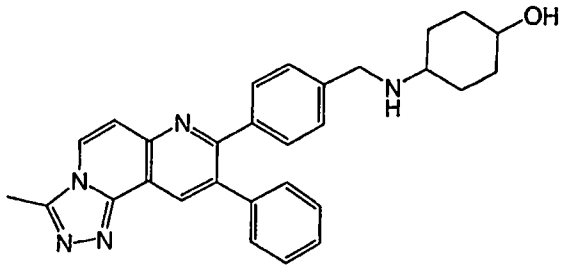
To a stirred solution of **13-2** (0.5g, 1.2mMol) and **8-5** (0.34g, 1.3mMol) in NMP (10mL) was added triethylamine (0.33mL, 2.3mMol) followed by acetic acid (0.13mL, 2.3mMol). After stirring overnight at room temperature, sodium triacetoxyborohydride (0.3g, 1.3mMol) was added in portions. After stirring for 6 hours, the solution was filtered through a syringe filter and purified on a C18 reverse phase HPLC to give **13-3** as a solid. Mass (M+1) calculated: 644.2993 observed: 644.2988

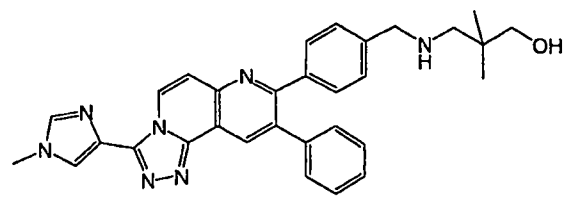
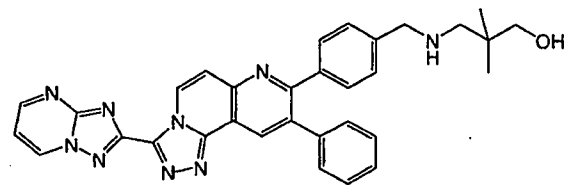
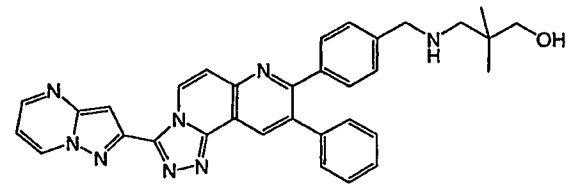
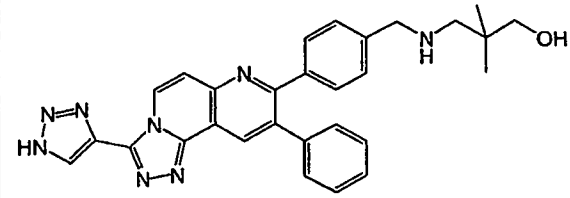
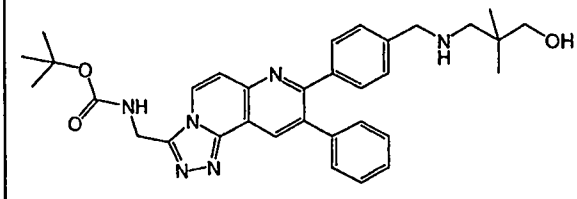
The following table (Table 4) contains compounds made using the procedures of Scheme 13, substituting the appropriate amine for **8-5**. Compounds **13-4** – **13-7**, **13-10** – **13-19** and **13-21** were isolated as the HCl salt. Compounds **13-8** and **13-9** were isolated as TFA salts.

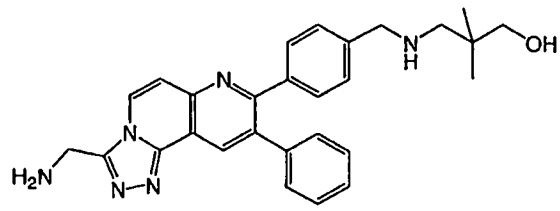
Table 4

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **13-4** |  | 3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine | 645.2946 |
| **13-5** |  | N-[2-(4-methyl-1H-imidazol-2-yl)ethyl]-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amine | 540.2609 |

| | | | |
|---|---|---|---|
| **13-6** |  | $N^1$-(2-hydroxyphenyl)-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-beta-alaninamide | 595.2564 |
| **13-7** |  | 1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide | 543.2611 |
| **13-8** |  | 5-[({4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amino)methyl]pyridin-2-ol | 539.2302 |
| **13-9** |  | $N^1$,$N^1$,2,2-tetramethyl-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propane-1,3-diamine | 545.3125 |
| **13-10** |  | 3-hydroxy-2,2-dimethyl-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine | Calc'd: 452.2659 Observed: 452.2655 |

| | | | |
|---|---|---|---|
| 13-11 |  | 2-fluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine | Calc'd: 442.2038 Observed: 442.2021 |
| 13-12 |  | 2,2-difluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine | Calc'd: 460.1944 Observed: 460.1926 |
| 13-13 |  | 2,3-dihydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine | Calc'd: 440.2081 Observed: 440.2076 |
| 13-14 |  | 4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine | Calc'd: 464.2445 Observed: 464.2448 |
| 13-15 |  | 4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine | Calc'd: 464.2445 Observed: 464.2438 |

| | | | |
|---|---|---|---|
| **13-16** |  | 3-hydroxy-2,2-dimethyl-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}propan-1-amine | Calc'd: 518.2663 Observed: 518.2663 |
| **13-17** |  | 3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine | Calc'd: 556.2568 Observed: 556.2570 |
| **13-18** |  | 3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine | Calc'd: 555.2616 Observed: 555.2575 |
| **13-19** |  | 3-hydroxy-2,2-dimethyl-N-{4-[9-phenyl-3-(1H-1,2,3-triazol-4-yl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propan-1-amine | Calc'd: 505.2459 Observed: 505.2453 |
| **13-20** |  | tert-butyl {[8-(4-{[(3-hydroxy-2,2-dimethylpropyl)amino]methyl}phenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}carbamate | Calc'd: 567.3018 Observed: 567.3015 |

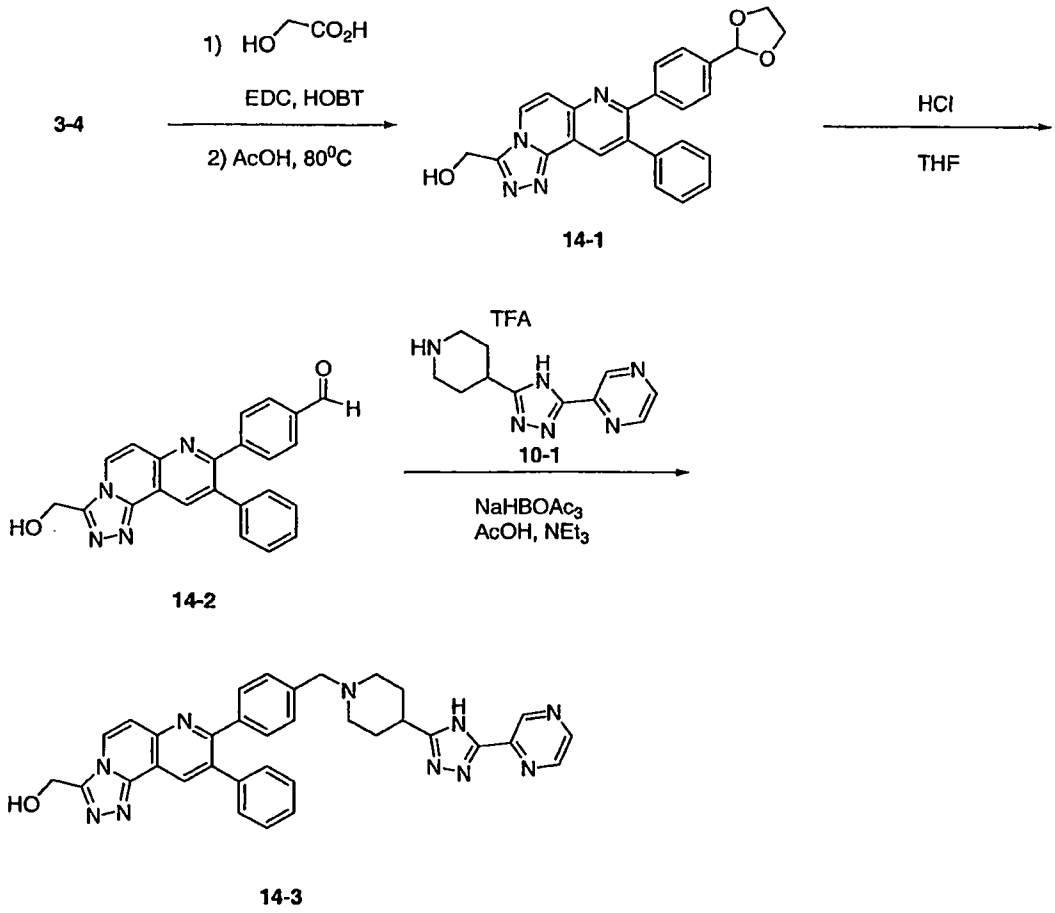
| | | | |
|---|---|---|---|
| 13-21 |  | N-{4-[3-(ammoniomethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-3-hydroxy-2,2-dimethylpropan-1-amine | Calc'd: 467.2554 Observed: 467.2553 |

Compound **13-4**

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**13-4**)

To a stirred solution of **13-2** (1.5g, 3.5mMol) and **10-1** (1.4g, 4.0mMol) in NMP (30mL) was added triethylamine (1mL, 7mMol) followed by acetic acid (0.4mL, 7mMol). After stirring overnight at room temperature, sodium triacetoxyborohydride (0.9g, 4.2mMol) was added in portions. After stirring for 6 hours, saturated $NaHCO_3$ solution was added until the pH was above 7. The resulting suspension was filtered and washed with water. The solid was dried azeotropically with toluene three times and was purified using normal phase flash chromatography (gradient: 100% $CHCl_3$ to 10% MeOH in $CHCl_3$ over 40min.) to yield **13-4** as a white solid. Mass (M+1) calculated: 645.2946 observed: 645.2946

SCHEME 14




[9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**14-3**)

{8-[4-(1,3-dioxolan-2-yl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol (**14-1**)

To a stirred solution of **3-4** (5g, 13mMol), HOBT (1.9g, 14.3mMol), and glycolic acid (1.2g, 15.6mMol) in anhydrous DMF (100mL) was added EDC (2.7g, 14.3mMol). The solution was stirred overnight at ambient temperature. The solution was then treated with 5mL of glacial acetic acid and was heated to 80°C in an oil bath for 2 hours. Upon cooling to room temperature, the reaction was diluted with ethyl acetate and washed with $NaHCO_{3\,(aq)}$, water, and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* to yield **14-1** as a red solid. LC/MS (M+1) calculated: 425.5; observed: 425.6

4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzaldehyde (**14-2**)

To a suspension of **14-1** (2.1g, 4.9mMol) in THF (50mL) was added 1N HCl (50mL). After stirring at room temperature for 30 minutes, the reaction was diluted with ethyl acetate and washed

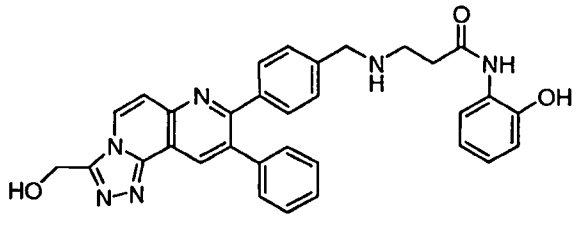
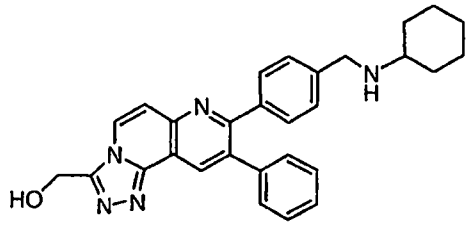
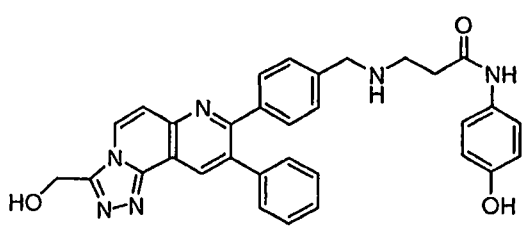
twice with water, followed by brine. The organic layer was dried with $MgSO_4$ and $Na_2SO_4$, filtered and concentrated *in vacuo* to yield **14-2** as a red solid. Mass (M+1) calculated: 381.1346 observed: 381.1346.

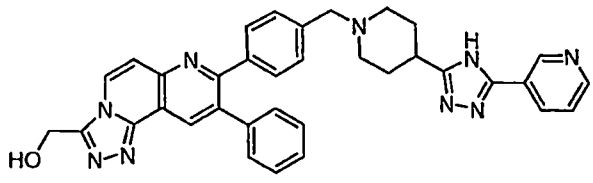
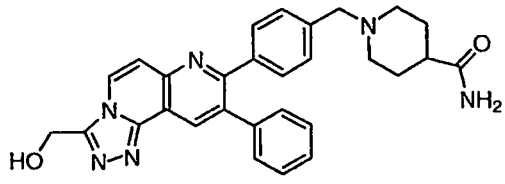
[9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol (**14-3**)

To a stirred solution of **14-2** (0.05g, 0.1mMol) and **10-1** (0.05g, 0.15mMol) in NMP (1mL) was added triethylamine (0.04mL, 0.26mMol) followed by acetic acid (0.01mL, 0.26mMol). After stirring overnight at room temperature, sodium triacetoxyborohydride (0.03g, 0.2mMol) was added. After stirring for 6 hours, the solution was filtered through a syringe filter and purified on a C18 reverse phase HPLC to give **14-3** as a solid. Mass (M+1) calculated: 595.2677 observed: 595.2679

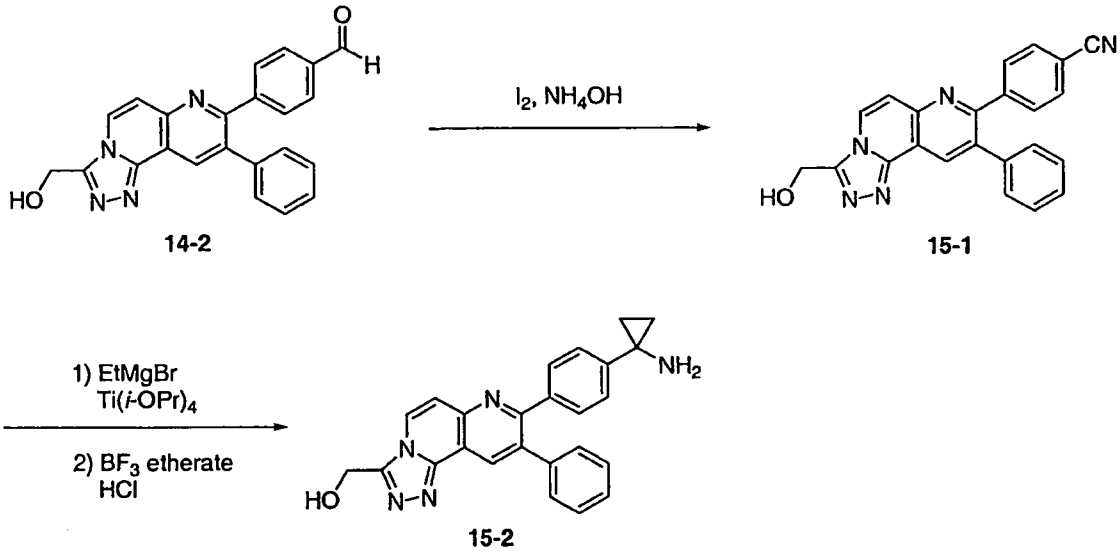
The following table (Table 5) contains compounds made using the procedures of Scheme 14, substituting the appropriate amine for **10-1**. Compounds **14-4**, **14-5**, **14-7** and **14-8** were isolated as HCl salts. Compound **14-6** was isolated as a TFA salt.

Table 5

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **14-4** |  | $N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(2-hydroxyphenyl)-beta-alaninamide | 545.2293 |
| **14-5** |  | (8-{4-[(cyclohexyl amino)methyl]phenyl}-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl)methanol | 464.2435 |
| **14-6** |  | $N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(4-hydroxyphenyl)-beta-alaninamide | 545.2296 |

| | | | |
|---|---|---|---|
| 14-7 |  | [9-phenyl-8-(4-{[4-(5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol | LRMS (M+1)= 594.2 |
| 14-8 |  | 1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide | 493.2344 |

SCHEME 15




14-2 15-1 15-2

{8-[4-(1-aminocyclopropyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol (15-2)

4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzonitrile (15-1)

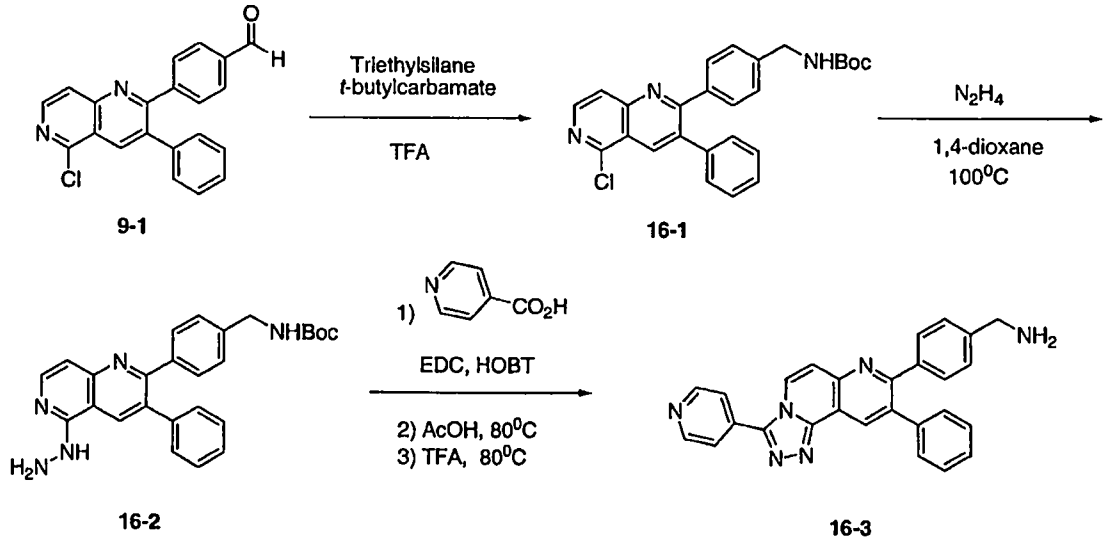
To a stirred suspension of **14-2** (0.4g, 1.1mMol) in anhydrous THF (15mL) was added 3mL of concentrated $NH_4OH$. The solution was then treated with iodine (0.4g, 1.6mMol) followed by stirring at room temperature overnight. The reaction was quenched with saturated sodium thiosulfate solution (20mL) and the product was extracted into ethyl acetate three times. The combined organic

layers were washed with brine, dried with $Na_2SO_4$, filtered and concentrated *in vacuo* to yield **15-1** as a tan solid. Mass (M+1) calculated: 378.135 observed: 378.1345

{8-[4-(1-aminocyclopropyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol (15-2)

Ethylmagnesium bromide in diethyl ether (0.4mL, 1.2mMol, 3M) was added at -70°C to a solution of **15-1** (0.1g, 0.3mmol) and titanium (IV) isopropoxide (0.17g, 0.6mMol) in anhydrous THF (7mL). After 10 min, the cold bath was removed and the reaction was warmed to room temperature. After stirring for 1 hour, more ethylmagnesium bromide in diethyl ether (0.18mL, 0.5mMol, 3M) was added and the reaction was cooled to 0°C in an ice bath and was treated with boron trifluoride etherate (0.18g, 1.2mMol). The reaction was stirred at 0°C for 30 minutes then warmed to room temperature for 1 hour. The reaction was quenched with 1N HCl followed by stirring for 3 hours. The solution was basified with 1M NaOH, extracted with chloroform, dried with $Na_2SO_4$, filtered and concentrated *in vacuo*. Crude residue was taken up in methanol and purified using a C18 reverse phase HPLC to give **15-2** as a solid. LC/MS (M+1) calculated: 408.4; observed: 408.0

SCHEME 16




1-[4-(9-phenyl-3-pyridin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (16-3)

*tert*-butyl 4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzylcarbamate (16-1)

To a stirred solution of **9-1** (7g, 20.2mMol) and *t*-butylcarbamate (2.6g, 22.3mMol) in dry acetonitrile (35mL) was added triethylsilane (29.1mL, 182mMol) followed by trifluoroacetic acid (6mL, 81mMol). After stirring for 3 hours, the solution was poured into aqueous $NaHCO_3$ and was extracted into ethyl acetate three times. The combined organic layers were washed with water followed by brine. The organic layer was then dried with $Na_2SO_4$, filtered, and concentrated *in vacuo* and purified using flash chromatography on silica. LC/MS (M+1) calculated: 446.9; observed: 446.1

*tert*-butyl 4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)benzylcarbamate (16-2)

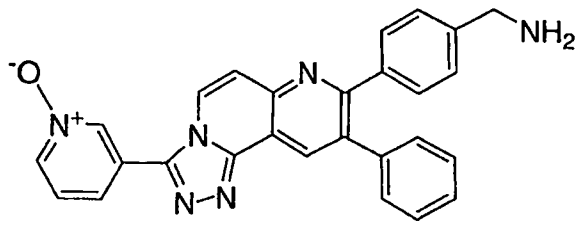
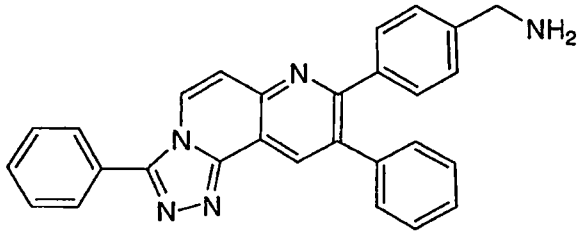
To a stirred solution of **16-1** (6.8g, 15.2mMol) in anhydrous 1,4-dioxane (20mL) was added hydrazine (10.8mL, 343mMol). The solution was heated to 100°C in a microwave reactor for 5 minutes. The solvent was removed *in vacuo* and the crude residue was taken up in ethyl acetate and washed with aqueous $NaHCO_3$ solution followed by brine. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo* to yield **16-2** as an orange solid. LC/MS (M+1) calculated: 442.5; observed: 442.2

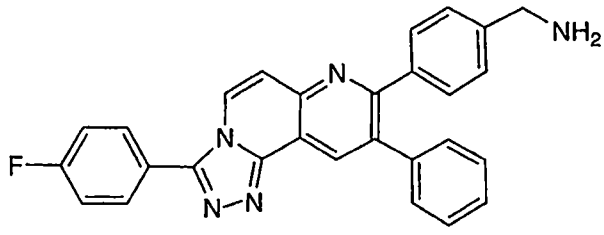
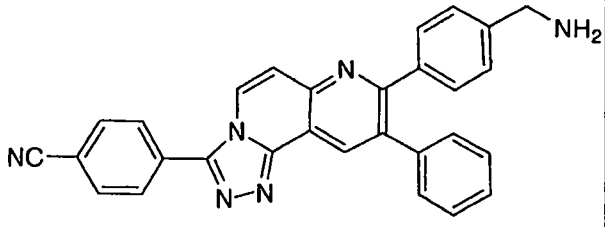
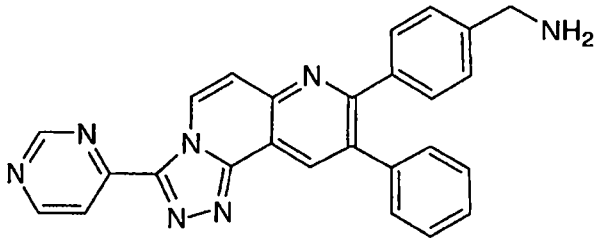
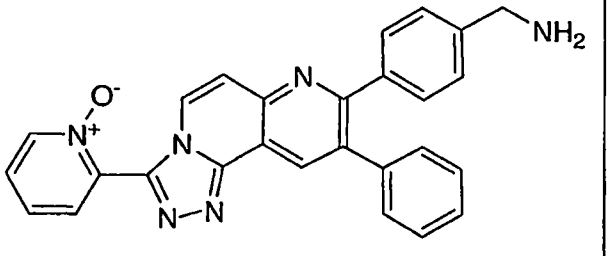
1-[4-(9-phenyl-3-pyridin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (**16-3**)

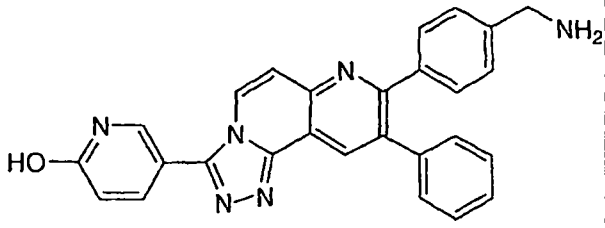
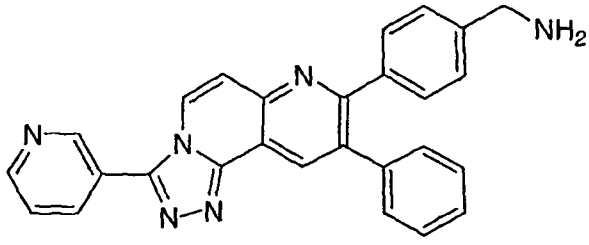
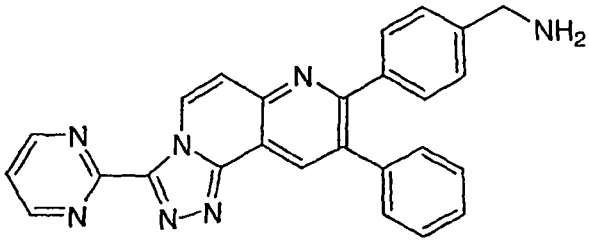
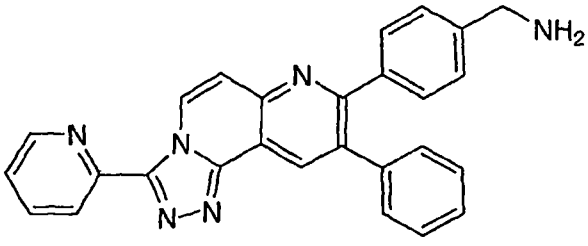
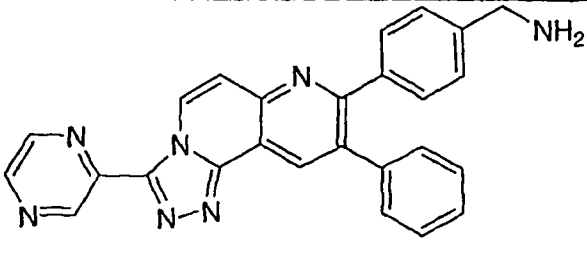
To a stirred solution of **16-2** (0.08g, 0.2mMol), HOBT (0.03g, 0.2mMol), and isonicotinic acid (0.02g, 0.2mMol) in anhydrous DMF (1mL) was added DIEA (0.08mL, 0.5mMol) followed by EDC (0.04g, 0.2mMol). The solution was heated in a microwave reactor at 80°C for 12min. The solution was then treated with 0.5mL of acetic acid and was heated in a microwave reactor at 80°C for 30 minutes. Upon cooling to room temperature, the volatiles were evaporated in vacuo and the solution was filtered through a syringe filter and purified on a C18 reverse phase HPLC to give **16-3** as a solid. Mass (M+1) calculated: 429.1822 observed: 429.1811

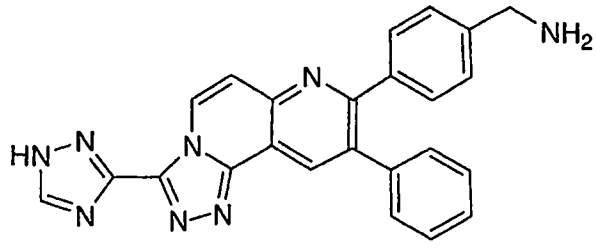
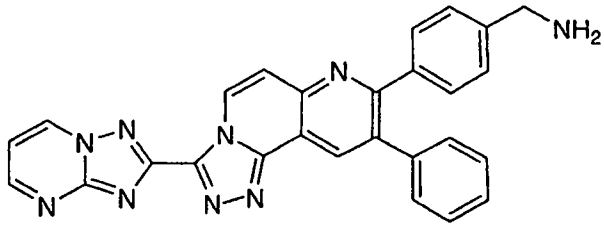
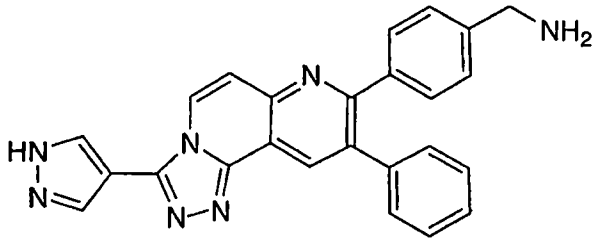
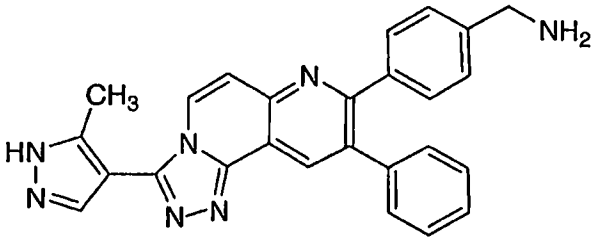
The following table (Table 6) contains compounds made using the procedures to of Scheme 16, substituting the appropriate carboxylic acid for isonicotinic acid:

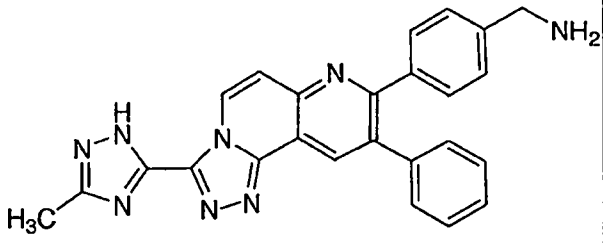
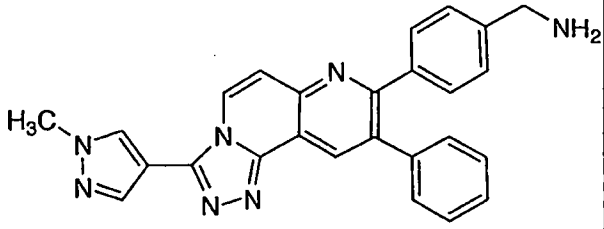
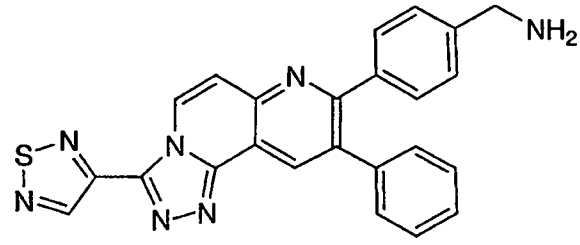
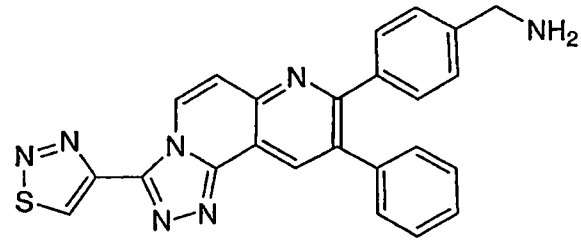
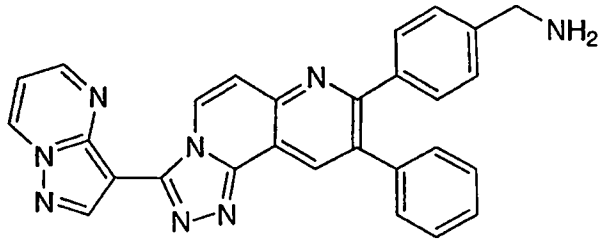
Table 6

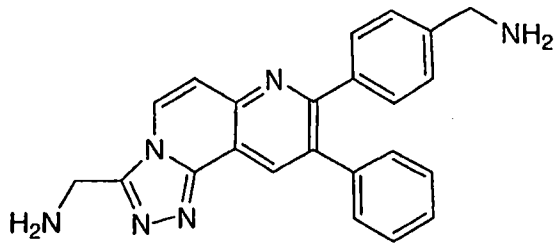
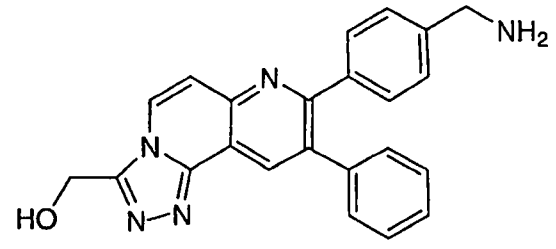
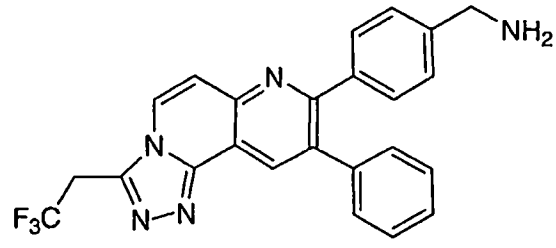
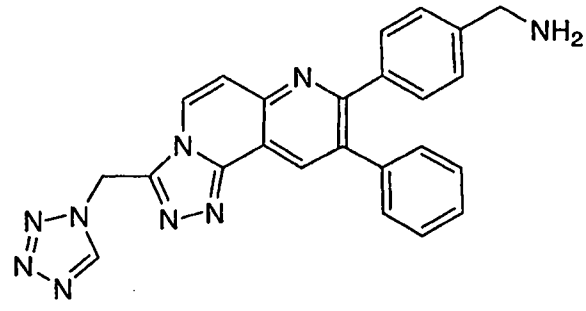
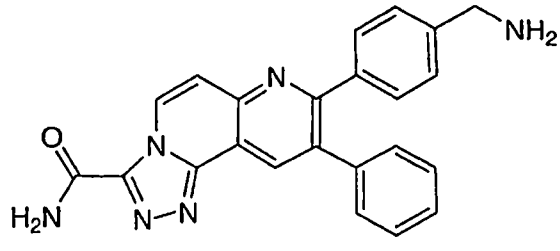
| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **16-4** |  | 1-{4-[3-(1-oxidopyridin-3-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] phenyl}methanamine; isolated as the HCl salt | 445.1772 |
| **16-5** |  | 1-[4-(3,9-diphenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the HCl salt | 428.1865 |

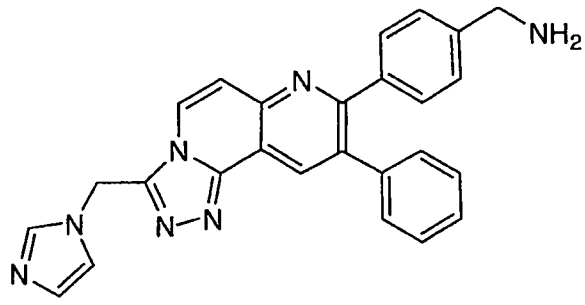
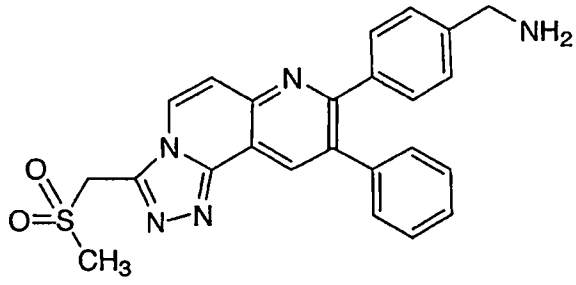
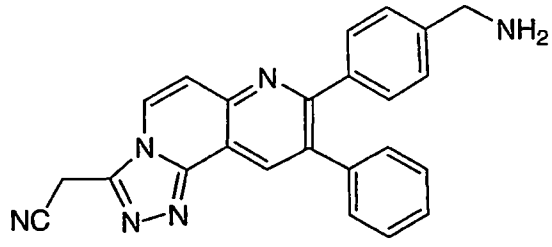
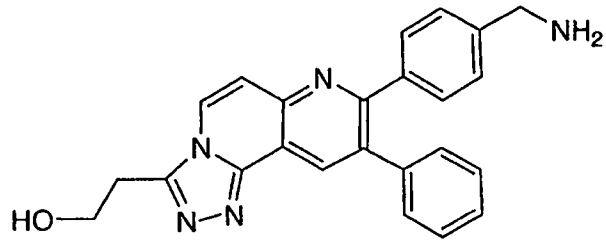
| | | | |
|---|---|---|---|
| **16-6** |  | 1-{4-[3-(4-fluorophenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 446.177 |
| **16-7** |  | 4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}benzonitrile; isolated as the HCl salt | 453.182 |
| **16-8** |  | 4-(9-phenyl-3-pyrimidin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine; isolated as the HCl salt | 430.1774 |
| **16-9** |  | 1-{4-[3-(1-oxidopyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 445.174 |

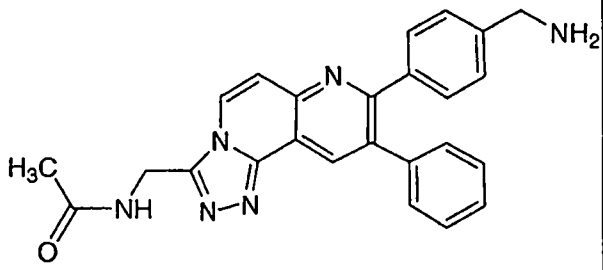
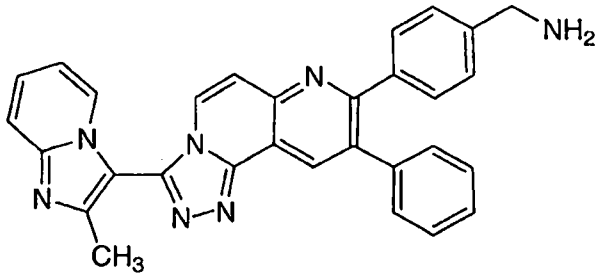
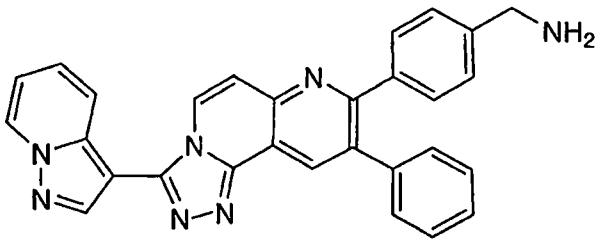
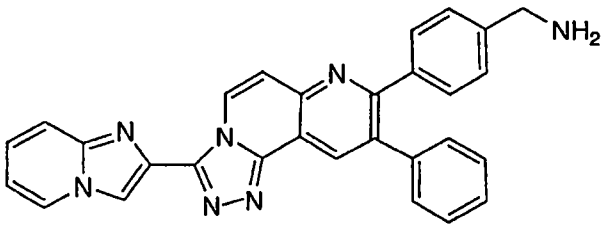
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|---|---|---|---|
| **16-10** |  | 5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}yridine-2-ol; isolated as the HCl salt | 445.1771 |
| **16-11** |  | 1-[4-(9-phenyl-3-pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the HCl salt | 429.1846 |
| **16-12** |  | 4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine; isolated as the HCl salt | 430.177 |
| **16-13** |  | 1-[4-(9-phenyl-3-pyridin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the TFA salt | LRMS (M+1)=429.1 |
| **16-14** |  | 1-[4-(9-phenyl-3-pyrazin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the HCl salt | 430.1775 |

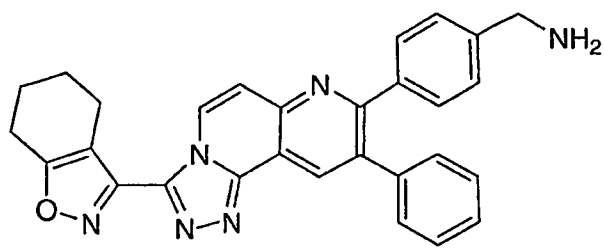
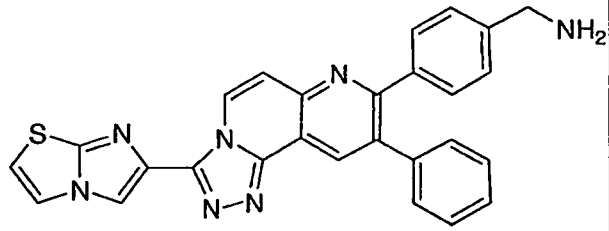
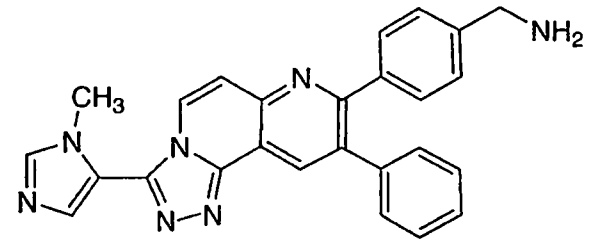
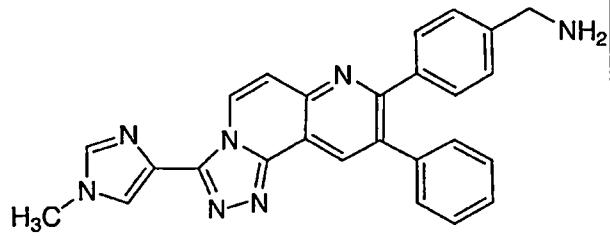
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| **16-15** |  | 1-{4-[9-phenyl-3-(1H-1,2,4-triazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 419.1727 |
| **16-16** |  | 1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 470.1824 |
| **16-17** |  | 1-{4-[9-phenyl-3-(1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 418.1764 |
| **16-18** |  | 1-{4-[3-(3-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 432.193 |

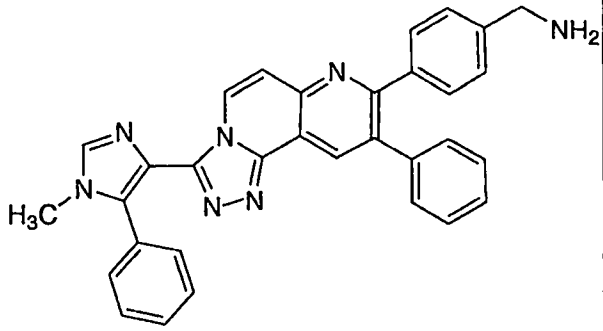
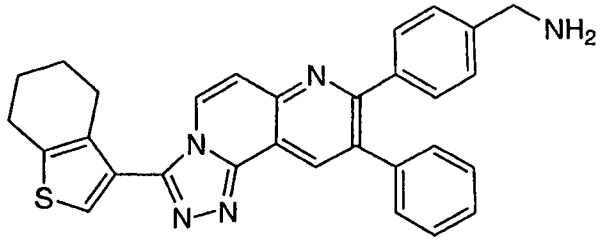
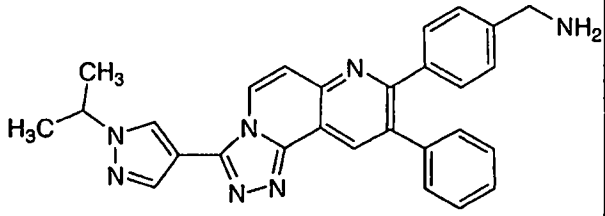
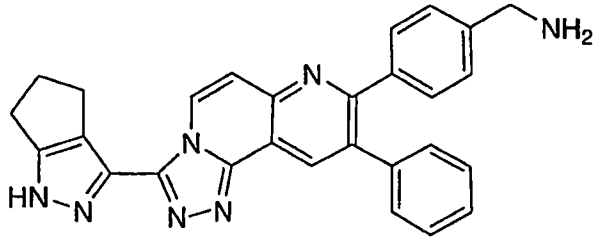
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| **16-19** |  | 1-{4-[3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 433.182 |
| **16-20** |  | 1-{4-[3-(1-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 432.193 |
| **16-21** |  | 1-{4-[9-phenyl-3-(1,2,5-thiadiazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 436.1341 |
| **16-22** |  | 1-{4-[9-phenyl-3-(1,2,3-thiadiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 436.1333 |
| **16-23** |  | 1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the HCl salt | 469.1882 |

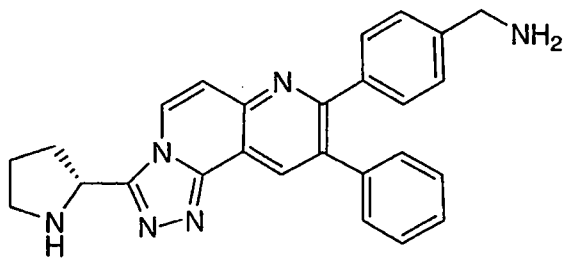
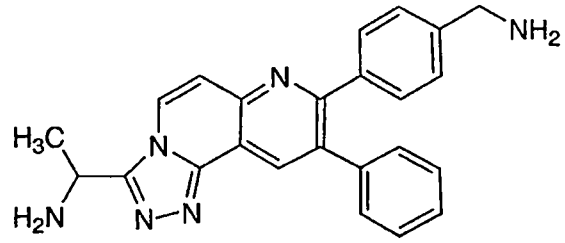
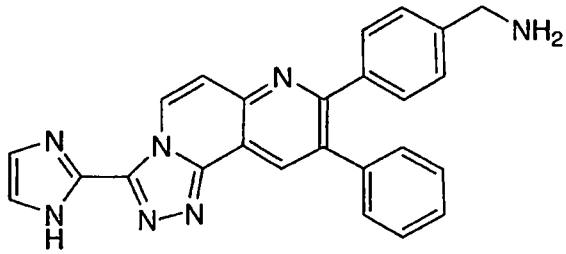
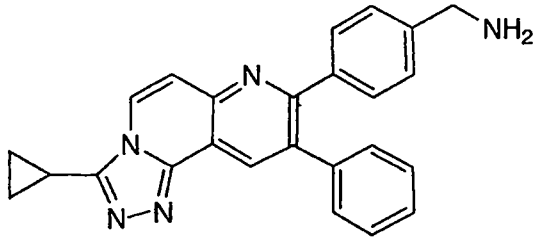
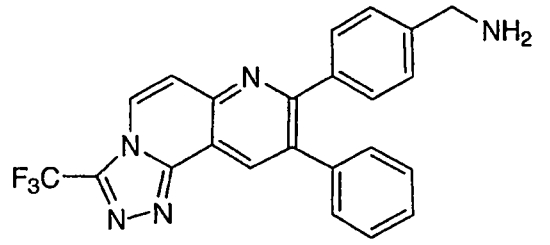
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| 16-24 |  | {8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanamine; isolated as the HCl salt | 381.1817 |
| 16-25 |  | {8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol; isolated as the HCl salt | 382.1657 |
| 16-26 |  | 1-{4-[9-phenyl-3-(2,2,2-trifluoroethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 434.1584 |
| 16-27 |  | 1-{4-[9-phenyl-3-(1H-tetraazol-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 434.1831 |
| 16-28 |  | 8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine-3-carboxamide; isolated as the HCl salt | LRMS (M+1)=395.2 |

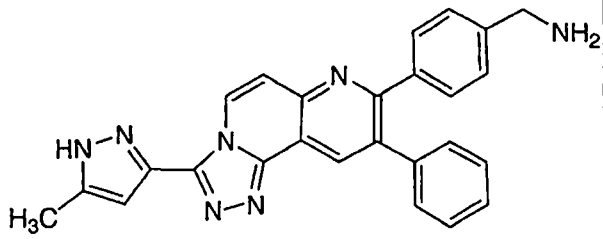
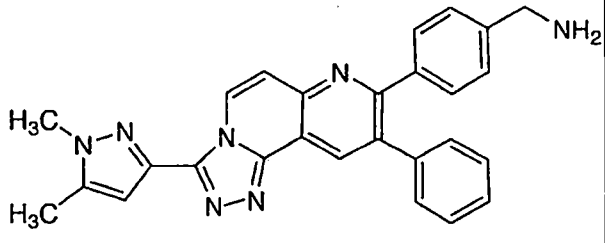
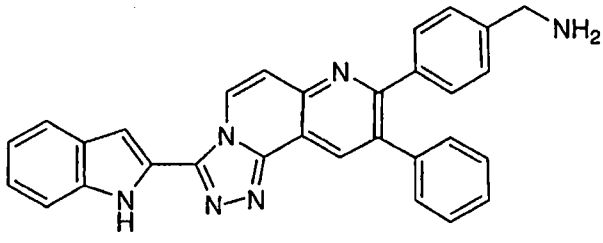
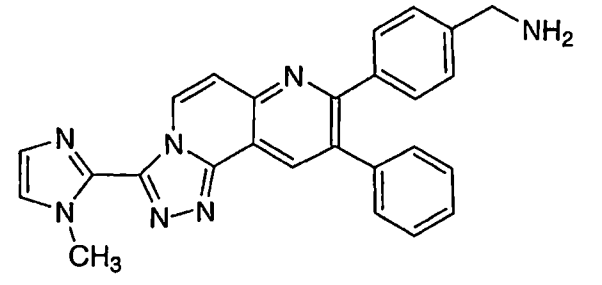
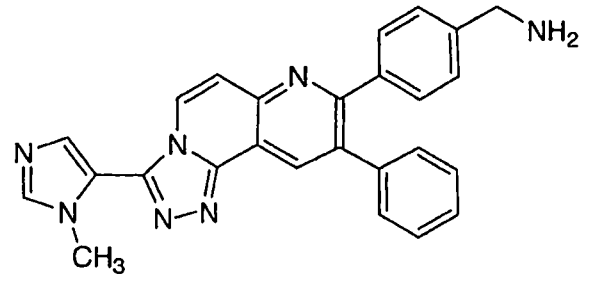
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| 16-29 |  | 1-{4-[3-(1H-imidazol-1-ylmethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 432.1931 |
| 16-30 |  | 1-(4-{3-[(methylsulfonyl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine; isolated as the HCl salt | 444.1488 |
| 16-31 |  | {8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}acetonitrile; isolated as the HCl salt | 391.166 |
| 16-32 |  | 2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol; isolated as the HCl salt | 396.1819 |

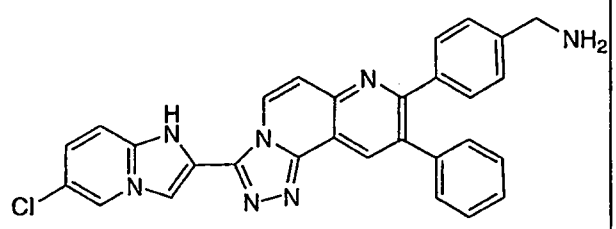
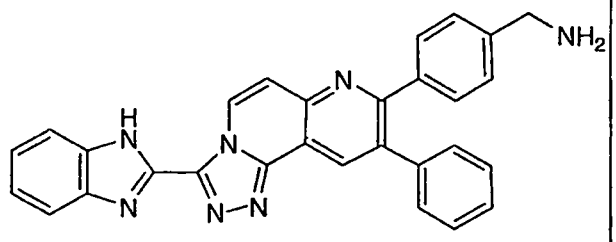
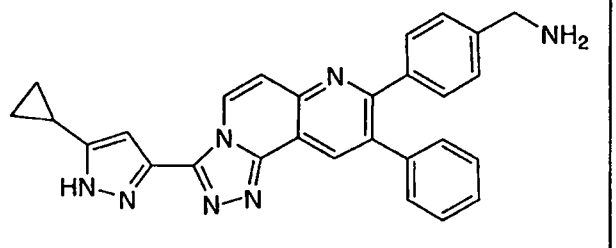
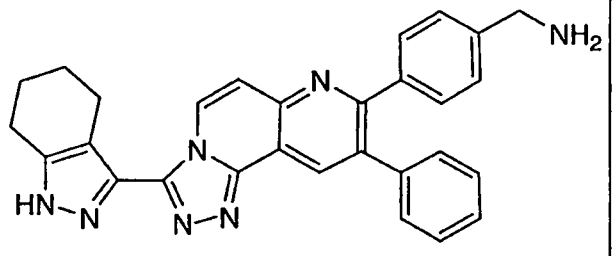
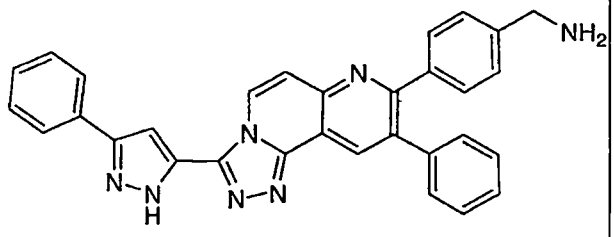
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| 16-33 |  | N-({8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methyl)acetamide; isolated as the HCl salt | 423.1925 |
| 16-34 |  | 4-[3-(2-methylimidazo[1,2-a]pyridin-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine | LRMS (M+1)=482.2 |
| 16-35 |  | 1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine | LRMS (M+1)=468.1 |
| 16-36 |  | 1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the free base and the HCl salt | 468.1923 |

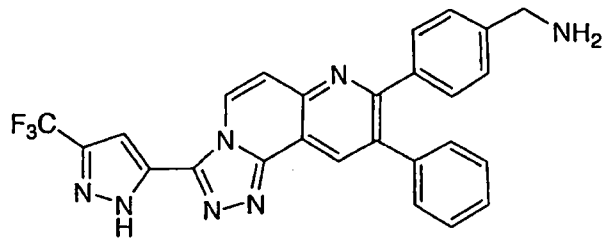
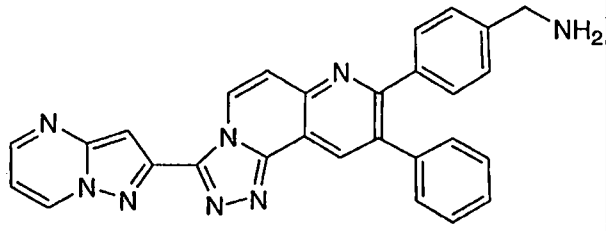
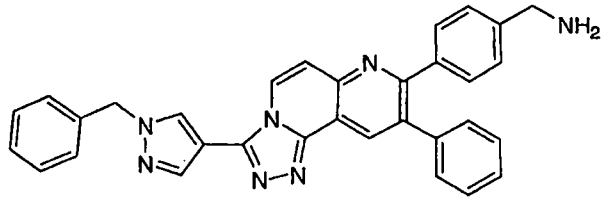
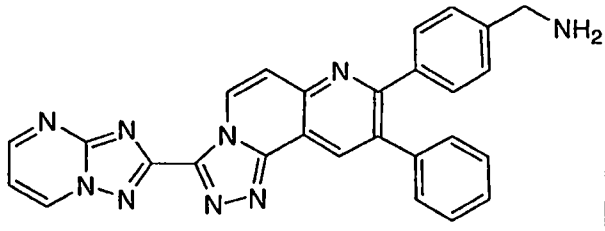
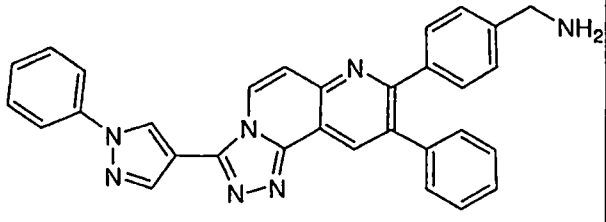
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| **16-37** |  | 1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | LRMS (M+1)=456.2 [M-NH2] |
| **16-38** |  | 1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the free base and the HCl salt | 474.1474 |
| **16-39** |  | 1-{4-[3-(1-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | LRMS (M+1)=415.1 [M-NH2] |
| **16-40** |  | 1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the free base and the HCl salt | LRMS (M+1)=432.1 |

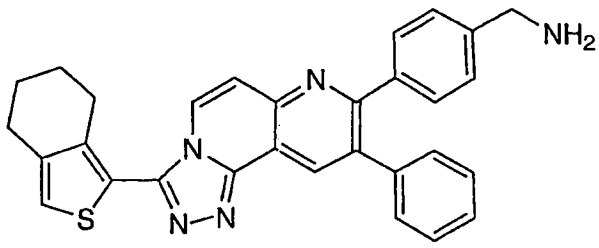
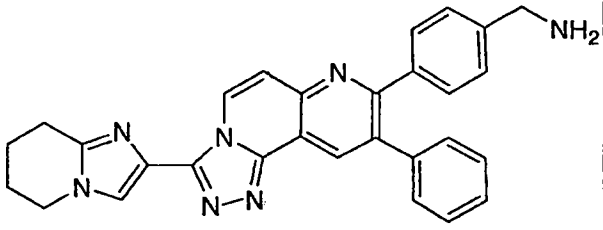
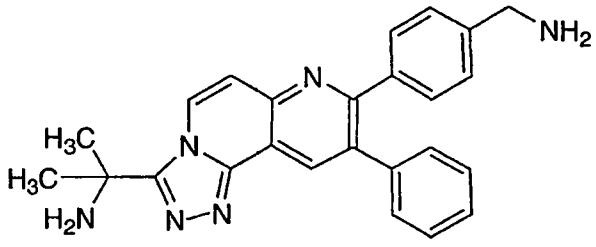
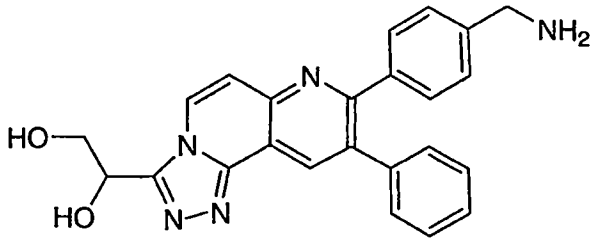
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| 16-41 |  | 4-[3-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the TFA salt | 508.2232 |
| 16-42 |  | 1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1-benzothien-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 488.189 |
| 16-43 |  | 1-{4-[3-(1-isopropyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 460.2245 |
| 16-44 |  | 1-{4-[9-phenyl-3-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 458.2067 |

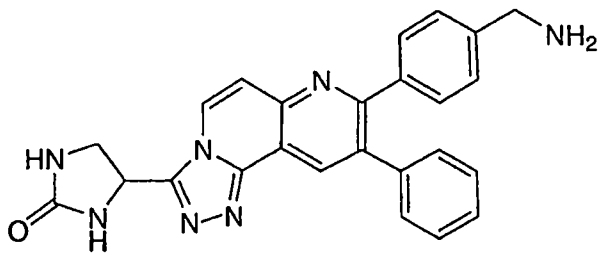
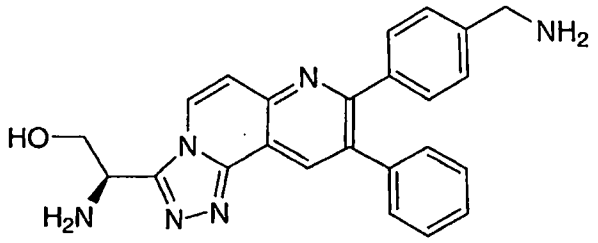
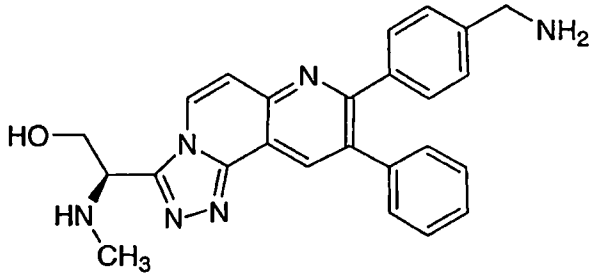
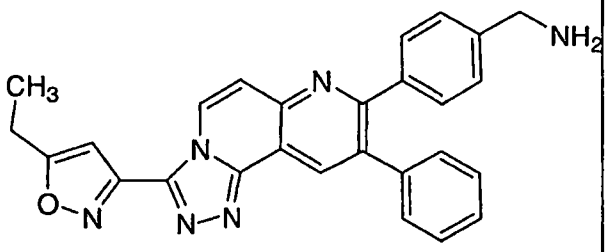
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| **16-45** |  | 1-(4-{9-phenyl-3-[(2S)-pyrrolidin-2-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine; isolated as the HCl salt | 421.2137 |
| **16-46** |  | 4-[3-(1-aminoethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the HCl salt | 395.1962 |
| **16-47** |  | 1-(4-[3-(1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 418.1774 |
| **16-48** |  | 1-[4-(3-cyclopropyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the TFA salt | 392.1866 |
| **16-49** |  | 1-{4-[9-phenyl-3-(trifluoromethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 420.1423 |

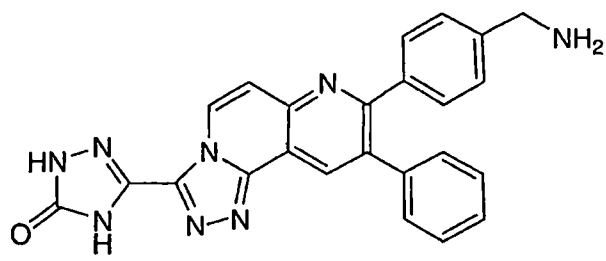
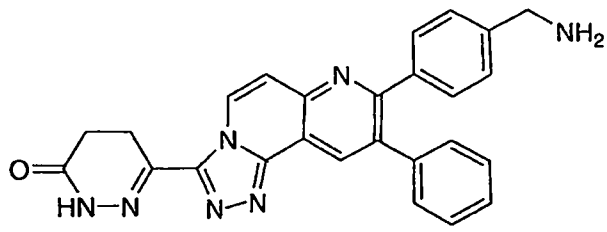
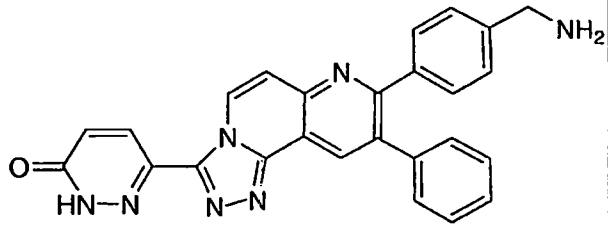
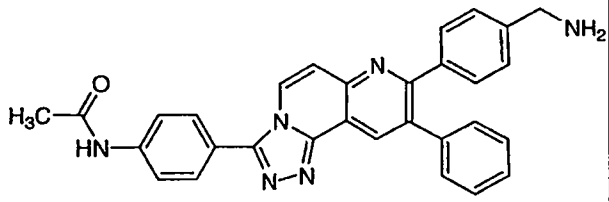
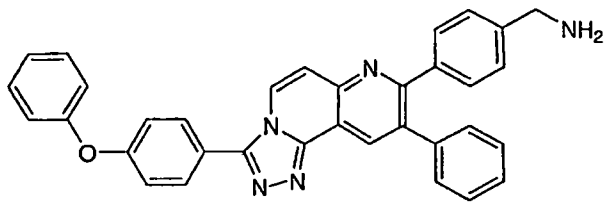
| | | | |
|---|---|---|---|
| 16-50 |  | 1-{4-[3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 432.1924 |
| 16-51 |  | 1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 446.2077 |
| 16-52 |  | 4-[3-(1H-indol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the TFA salt | 467.1968 |
| 16-53 |  | 1-{4-[3-(1-methyl-1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 432.1921 |
| 16-54 |  | 1-{4-[3-(3-methyl-2H-3lambda$^5$-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | LRMS (M+1)=432.1 |

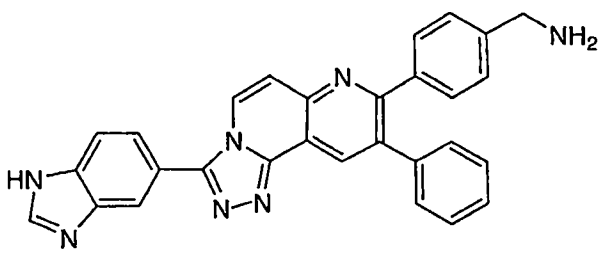
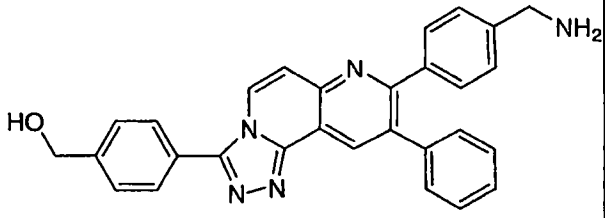
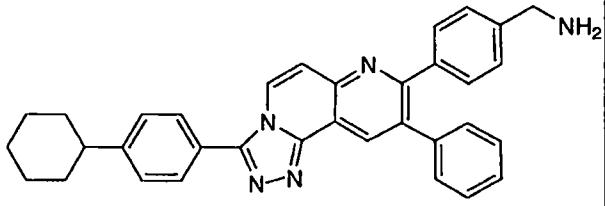
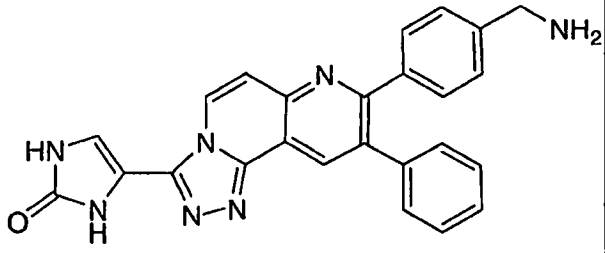
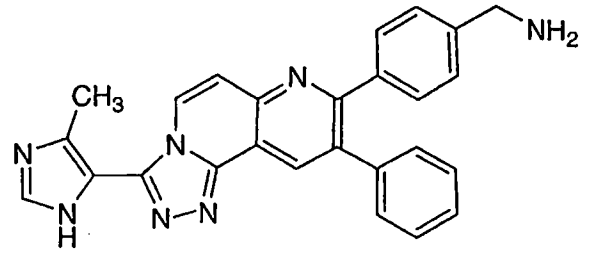
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| 16-55 |  | 4-[3-(6-chloroimidazo[1,2-a]pyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the TFA salt | LRMS (M+1)=502.1 |
| 16-56 |  | 1-{4-[3-(1H-benzimidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 468.1921 |
| 16-57 |  | 4-[3-(5-cyclopropyl-4H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the TFA salt | 458.2087 |
| 16-58 |  | 1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1H-indazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 472.2244 |
| 16-59 |  | 4-[9-phenyl-3-(3-phenyl-1H-pyrazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the TFA salt | 494.2085 |

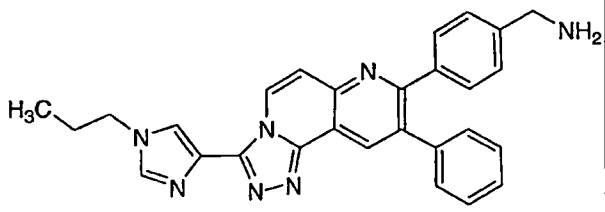
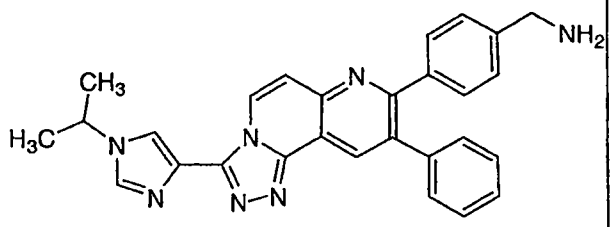
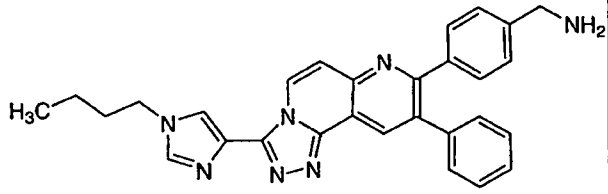
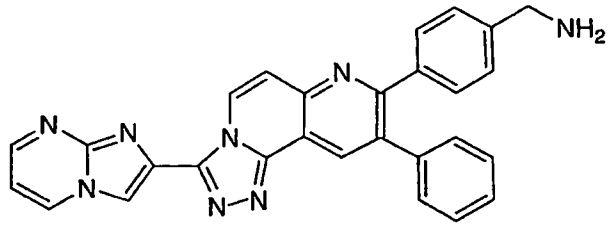
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| **16-60** |  | 1-(4-{9-phenyl-3-[3-(trifluoromethyl)-1H-pyrazol-5-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine; isolated as the TFA salt | 486.1643 |
| **16-61** |  | 1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the TFA salt | 469.1881 |
| **16-62** |  | 1-{4-[3-(1-benzyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 508.2235 |
| **16-63** |  | 1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the TFA salt | 470.1834 |
| **16-64** |  | 4-[9-phenyl-3-(1-phenyl-1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the TFA salt | 494.2085 |

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|---|---|---|---|
| **16-65** |  | 1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-2-benzothien-1-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the TFA salt | 488.1901 |
| **16-66** |  | 1-{4-[9-phenyl-3-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 472.2231 |
| **16-67** |  | 2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}propan-2-amine; isolated as the HCl salt | 409.2126 |
| **16-68** |  | 1-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethane-1,2-diol; isolated as the TFA salt | 412.1761 |

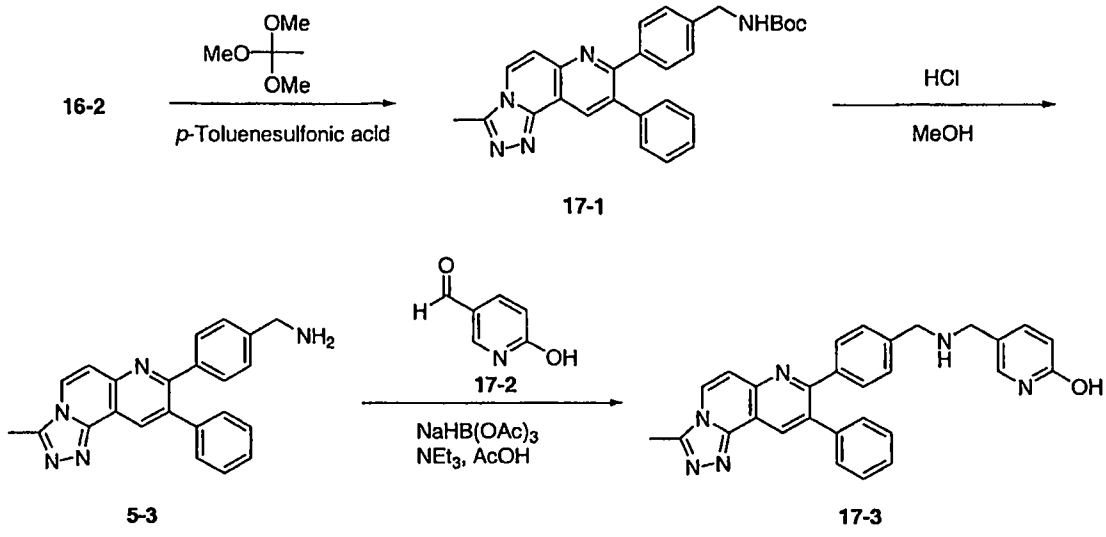
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| **16-69** |  | 4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}imidazolidin-2-one; isolated as the TFA salt | 436.1873 |
| **16-70** |  | (2R)-2-amino-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol; isolated as the TFA salt | 411.1921 |
| **16-71** |  | (2R)-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2-(methylamino)ethanol; isolated as the TFA salt | 425.2077 |
| **16-72** |  | 1-{4-[3-(5-ethylisoxazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 447.1913 |

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|---|---|---|---|
| 16-73 |  | 5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2,4-dihydro-3H-1,2,4-triazol-3-one; isolated as the HCl salt | LRMS (M+1)=435.2 |
| 16-74 |  | 6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-4,5-dihydropyridazin-3(2H)-one; isolated as the HCl salt | LRMS (M+1)=431.2 [M-NH2] |
| 16-75 |  | 6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}pyridazin-3(2H)-one; isolated as the HCl salt | LRMS (M+1)=429.1 [M-NH2] |
| 16-76 |  | N-(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)acetamide; isolated as the HCl salt | 485.2074 |
| 16-77 |  | 1-{4-[3-(4-phenoxyphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 520.2136 |

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|---|---|---|---|
| 16-78 |  | 1-{4-[3-(1H-benzimidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 468.1927 |
| 16-79 |  | (4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)methanol; isolated as the HCl salt | 458.1963 |
| 16-80 |  | 4-[3-(4-cyclohexylphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as a HCl salt | 510.2634 |
| 16-81 |  | 4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-1,3-dihydro-2H-imidazol-2-one; isolated as a HCl salt | 434.1719 |
| 16-82 |  | 1-{4-[3-(4-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 432.1921 |

| | | | |
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| **16-83** |  | 4-[9-phenyl-3-(1-propyl-1H-imidazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine; isolated as the HCl salt | 460.2231 |
| **16-84** |  | 1-{4-[3-(1-isopropyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 460.2231 |
| **16-85** |  | 1-{4-[3-(1-butyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine; isolated as the HCl salt | 474.2387 |
| **16-86** |  | 1-[4-(3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine; isolated as the HCl salt | 469.1867 |

SCHEME 17




5-({[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] amino}methyl)pyridin-2-ol (17-3)

*tert*-butyl 4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylcarbamate (17-1)

To a stirred solution of **16-2** (5g, 11.3mMol) in 20mL of 3:1 toluene:methanol was added trimethyl orthoacetate (1.8g, 15.3mMol) and *p*-toluenesulfonic acid monohydrate (0.1g, 0.6mMol). The reaction was heated to 100°C in a microwave reactor for 35 minutes. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified using normal phase flash chromatography to yield **17-1** as a solid. LC/MS (M+1) calculated: 466.6 observed: 466.2

1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine (5-3)

$HCl_{(g)}$ was bubbled through methanol (75mL) for 5 min. To this solution, **17-1** (7.5g, 16mmMol) was added and the solution was stirred at room temperature for 6 hours. After removing the solvent *in vacuo*, the resulting solid was triturated for 30 minutes with a 10:1 solution of ethyl acetate and methanol, repectively. The suspension was filtered and dried to yield 5-3 as the HCl salt. Mass (M+1) calculated: 366.1713 observed: 366.1694

6-hydroxynicotinaldehyde (17-2)

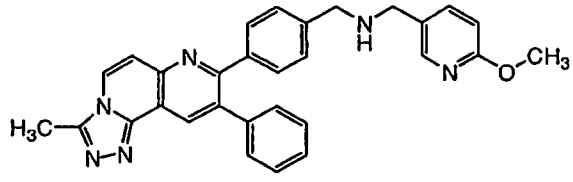
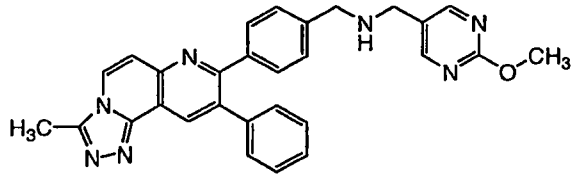
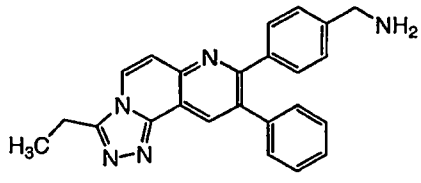
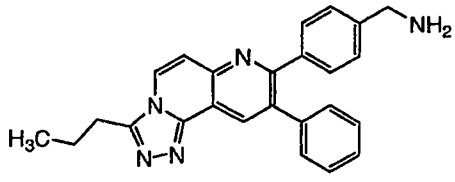
A stirred solution of 6-methoxy-3-pyridinecarboxaldehyde (0.45g, 3.3mMol) in 3N HCl (10mL) was heated to 100°C for 30 minutes. Upon cooling, needle-like crystals developed. The crystals were collected via filtration to yield **17-2**. $^1$H-NMR ($CD_3OD$) δ 9.64 (s, 1H), δ 8.17-8.16 (m, 1H), δ 7.96-7.94 (m, 1H), δ 6.58(d, 1H).

5-({[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] amino}methyl)pyridin-2-ol (17-3)

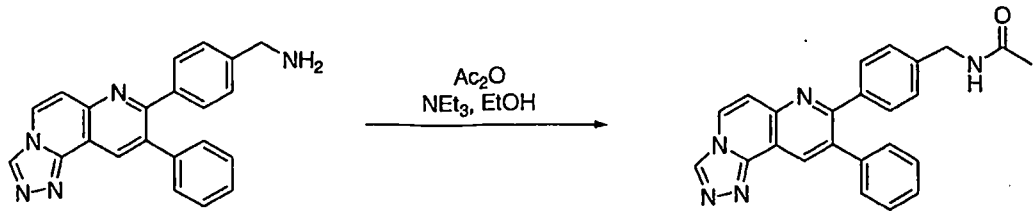
To a stirred solution of 5-3 (0.1g, 0.3mMol) and triethylamine (0.08mL, 0.5mMol) in NMR (1mL) was added 17-2 (0.03g, 0.3mMol) and acetic acid (0.03mL, 0.5mMol), followed by sodium triacetoxyborohydride (0.12g, 0.5mMol). After stirring overnight at room temperature, the reaction was filtered through a syringe filter and purified on a C18 reverse phase HPLC to yield **17-3** as the HCl salt. Mass (M+1) calculated: 473.2085 observed: 473.2092.

The following table (Table 7) contains compounds made using the procedures of Scheme 17, substituting the appropriate aldehyde for **17-2**. Compounds **17-4** and **17-5** were isolated as HCl salts. Compounds **17-6** and **17-7** were isolated as TFA salts.

Table 7

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **17-4** |  | 1-(6-methoxypyridin-3-yl)-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]methanamine | 487.2237 |
| **17-5** |  | N-[(2-methoxypyrimidin-5-yl)methyl]-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amine | LRMS (M+1)= 488.1 |
| **17-6** |  | 1-[4-(3-ethyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine | LRMS (M+1)= 380.2 |
| **17-7** |  | 1-[4-(9-phenyl-3-propyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine | 394.2023 |

SCHEME 18

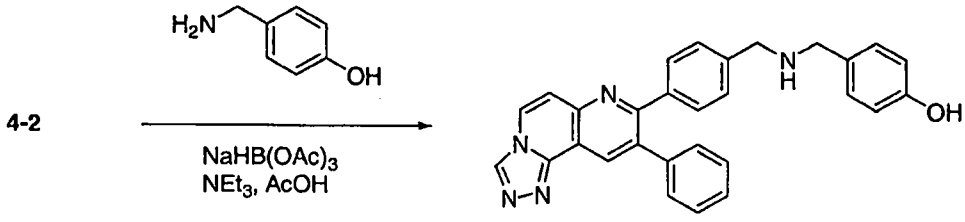



4-3 18-1

N-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] acetamide (18-1)

To a solution of 4-3 (0.02g, 0.06mMol) and triethylamine (0.02mL, 0.2mMol) in absolute ethanol (0.5mL) was added acetic anhydride (0.02mL, 0.2mMol). The reaction was complete after 10 minutes and was purified directly on a C18 reverse phase HPLC to give **18-1** as a solid. LC/MS (M+1) calculated: 394.5; observed: 394.2

SCHEME 19

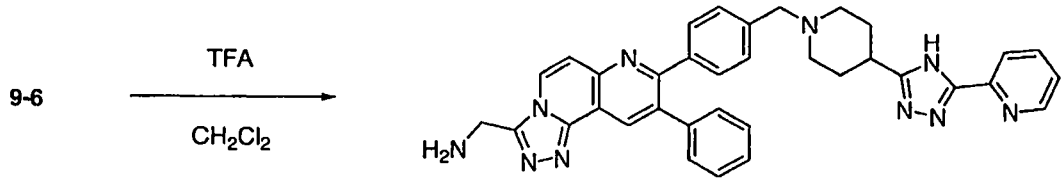



19-1

4-({[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amino} methyl)phenol (19-1)

To a stirred solution of 4-2 (0.05g, 0.14mMol) and 4-(aminomethyl)phenol (0.04, 0.35mMol) in DMF (0.5mL) was added acetic acid (0.04mL, 0.7mMol). After stirring for 2 hours at room temperature, sodium triacetoxyborohydride (0.06g, 0.3mMol) was added. After stirring overnight, the reaction was filtered through a syringe filter and purified on a C18 reverse phase HPLC to yield **19-1** as a solid. LC/MS (M+1) calculated: 458.5; observed: 458.3.

SCHEME 20

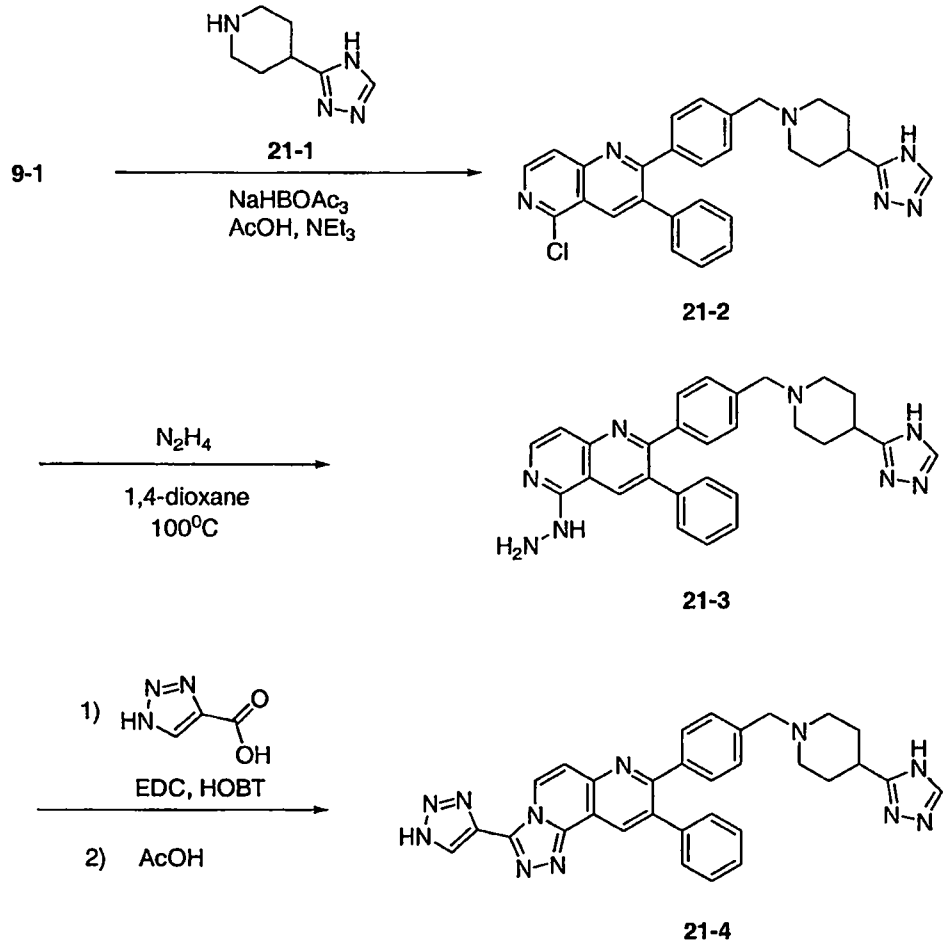



20-1

1-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl] methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanamine (**20-1**)

A solution of **9-6** (0.03g, 0.04mMol) in 30% TFA in dichloromethane (1mL, 30% by volume) was stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and the crude residue was taken up in methanol and purified on a C18 reverse phase HPLC to give **20-1** as a solid. Mass (M+1) calculated: 593.2884; observed: 593.2867.

SCHEME 21




9-phenyl-3-(1H-1,2,3-triazol-4-yl)-8-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**21-4**)

4-(1*H*-1,2,4-triazol-3-yl)piperidine (**21-1**)

To a solution of benzyl 4-cyanopiperidine-1-carboxylate (20 g, 82 mmol) in methanol (150 mL) was added a solution of sodium methoxide in methanol (25wt%, 5.6 mL, 25 mmol) at room temperature. After 30 minutes, a solution of formic hydrazide (4.9 g, 82 mmol) in methanol (20 mL) was added and the reaction was heated to reflux for 24 hours, at which time sodium methoxide in methanol (25wt%, 5.6 mL, 25 mmol) and formic hydrazide (4.9 g, 82 mmol) was added. After 72 hours, the

reaction was cooled to room temperature and quenched with acetic acid (3.0 mL, 49 mmol) and concentrated. The resulting residue was dissolved in ethyl acetate, washed with water, saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography eluting with 1-35% IPA/DCM. The appropriate fractions were combined and the solvent removed in vacuo to give benzyl 4-(1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate as a solid. MS ($M+H^+$): 287.2; $^1$H-NMR (400 MHz, $CDCl_3$): δ 11.13 (s, 1H), 8.06 (s, 1H), 7.36-7.31 (m, 5H), 5.15 (s, 2H), 4.24 (br.s, 2H), 3.06-2.98 (m, 3H), 2.07-2.04 (m, 2H), 1.84-1.78 (m, 2H).

To a solution of benzyl 4-(1*H*-1,2,4-triazol-3-yl)piperidine-1-carboxylate (7.3 g, 25 mmol) in ethanol (100 mL) was added 10% palladium on carbon (500 mg) and the reaction vessel was purged with hydrogen and stirred over an atmosphere of hydrogen for 3 hours. The reaction was filtered and concentrated to give **21-1** as a solid. MS ($M+H^+$): 153.2; $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 7.99 (s, 1H), 2.98-2.94 (m, 2H), 2.82-2.74 (m, 1H), 2.57-2.50 (m, 2H), 1.82-1.78 (m, 2H), 1.60-1.50 (m, 2H).

5-chloro-3-phenyl-2-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (21-2)

To a stirred solution of **9-1** (0.25g, 0.73mMol) and **21-1** (0.13g, 0.87mMol) in NMP (5mL) was added triethylamine (0.3mL, 2.2mMol) followed by acetic acid (0.082mL, 1.5mMol). After stirring at ambient temperature overnight, sodium triacetoxyborohydride (0.18g, 0.87mMol) was added. Upon completion, the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, followed by water, then brine. The organic layer was dried with $Na_2SO_4$ and $MgSO_4$, filtered and concentrated *in vacuo* to yield **21-2**. LC/MS (M+1) calculated: 482.0; observed: 482.2

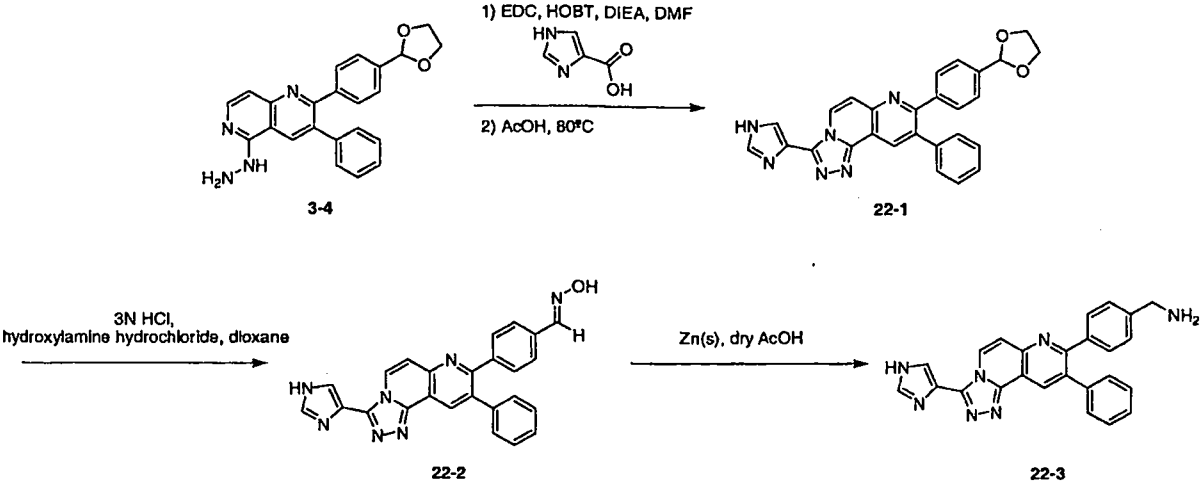
5-hydrazino-3-phenyl-2-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-1,6-naphthyridine (21-3)

To a stirred solution of **21-2** (0.4g, 0.8mMol) in anhydrous 1,4-dioxane (3mL) was added hydrazine (0.45mL, 14.5mMol). The solution was heated to 100°C in a microwave reactor for 5 minutes. The solvent was removed *in vacuo* and was dried azeotropically with toluene three times to yield **21-3**. LC/MS (M+1) calculated: 477.6; observed: 477.3

9-phenyl-3-(1H-1,2,3-triazol-4-yl)-8-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (21-4)

To a stirred solution of **21-3** (0.2g, 0.36mMol), HOBT (0.05g, 0.4mMol), and 1H-1,2,3-triazole-4-carboxylic acid (0.05g, 0.4mMol) in anhydrous DMF (2mL) was added DIEA (0.18mL, 1.1mMol) followed by EDC (0.08g, 0.4mMol). The solution was heated in the microwave reactor for 12 minutes at 80°C. The solution was then treated with 0.5mL of acetic acid and was heated to 80°C in the microwave reactor for and additional 10 minutes. Upon cooling to room temperature, the solution was passed through a syringe filter and purified on a C18 reverse phase HPLC to yield **21-4** as the HCl salt. Mass (M+1) calculated: observed: LC/MS (M+1) calculated: 554.6; observed: 554.3.

SCHEME 22




1-{4-[3-(1H-Imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-3**)

8-[4-(1,3-Dioxolan-2-yl)phenyl]-3-(1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine (**22-1**)

To a solution of **3-4** (0.2g, 0.5mmol), 1H-imidazole-4-carboxylic acid (0.06g, 0.5mmol), HOBT (0.06g, 0.5mmol), and DIEA (0.2ml, 1.4mmol) in DMF (2ml) was added EDC (0.1g, 0.6mmol). The solution was stirred at room temperature for 45min and was then heated at 80°C in the microwave for 15min. The solvent was removed in vacuo. The residue was taken up in DMF (0.5ml) and was treated with glacial AcOH (2.0ml). The reaction mixture was heated at 80°C for 45min. The reaction was then quenched with water (10ml) and extracted into EtOAc (3x20ml). The combined organic layers were concentrated in vacuo to give **22-1** as a brown residue.

MS calculated M+H: 461.5, found 461.2

4-[3-(1H-Imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzaldehyde oxime (**22-2**)

To a solution of **22-1** (0.8g, 1.7mmol) in 1,4-dioxane (3ml) was added 3N HCl (1.1ml, 3.4mmol) dropwise. After stirring for 10min the solution was treated with hydroxylamine hydrochloride (0.5g, 6.9mmol) in water (0.5ml). The mixture was stirred for 1h and was then quenched with $NaHCO_3$(s) until pH=8. Upon solvent removal the residue was taken up in water, filtered, and dried azeotropically with toluene to afford **22-2** as a solid.

MS calculated M+H: 432.5, found 432.2

1-{4-[3-(1H-Imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine (**22-3**)

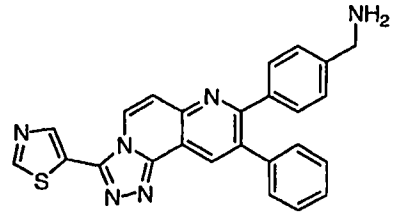
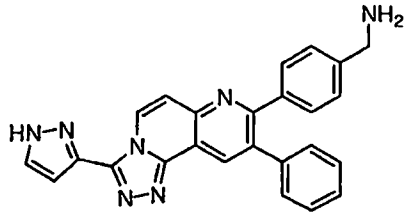
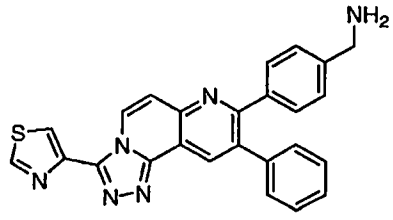
A solution of **22-2** (0.06, 0.1mmol) and Zn(s) (0.02g, 0.3mmol) in dry glacial AcOH was stirred at room temperature for 30min. To the solution was added another 4 equivalents of Zn(s) (0.04g,

0.6mmol). The reaction mixture was stirred for an additional 1h. After filtration and solvent removal the residue was taken up in MeOH and was treated with ammonium hydroxide. Upon solvent removal, the residue was purified by reverse phase HPLC to give **22-3** as a solid.

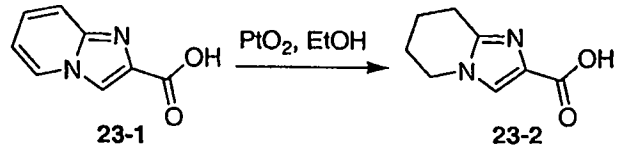
MS calculated M+H: 418.5, found 401.1 ($M-NH_2$)

The following table (Table 8) contains compounds made using the procedures of Scheme 22 substituting the appropriate acid for the imidazole-4-carboxylic acid. The compounds in Table 8 were isolated as the HCl salt.

Table 8

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **22-4** |  | 1-{4-[9-phenyl-3-(3H-1lambda$^4$,3-thiazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | 437.1543 |
| **22-5** |  | 1-{4-[9-phenyl-3-(1H-pyrazol-3-yl)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | 418.1776 |
| **22-6** |  | 1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | 435.1385 |

SCHEME 23

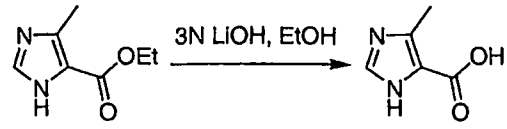



**23-1** **23-2**

5,6,7,8-Tetrahydroimidazo[1,2-a]pyridine-2-carboxylic acid (**23-2**)

To a solution of **23-1** (0.1g, 0.7mmol) in EtOH (15ml) in a dried flask was added $Pt_2O$ (0.1g, 0.4mmol). The reaction mixture was placed under a nitrogen atmosphere and was subsequently evacuated. This was repeated 3 times before placing the reaction mixture under an atmosphere of hydrogen. After 3h the reaction mixture was filtered through celite. Upon solvent removal the desired product **23-2** was obtained as an off-white powder. MS calculated M+H: 167.2, found 167.1

SCHEME 24

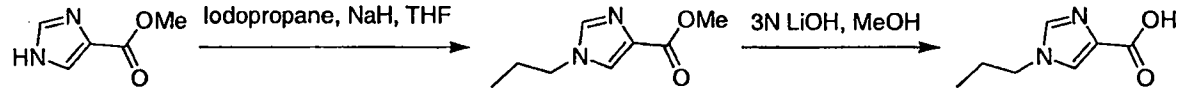



**24-1** **24-2**

4-Methyl-1H-imidazole-5-carboxylic acid (**24-2**)

To a solution of **24-1** (0.5g, 2.4mmol) in EtOH (2ml) was added 3N LiOH (2.2ml, 6.5mmol). The reaction mixture was heated at 80°C for 1h. The heat was reduced to 40°C and the mixture was stirred overnight. The mixture was then heated at 80°C for an additional 5.5h. The reaction was neutralized with 12N HCl and was concentrated in vacuo. The residue was dried azeotropically with toluene to afford the desired product **24-2** as a solid. MS calculated M+H: 127.1, found 127.1

SCHEME 25




**25-1** **25-2** **25-3**

Methyl 1-propyl-1H-imidazole-4-carboxylate (**25-2**)

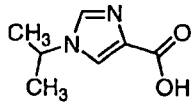
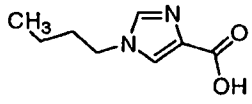
To a solution of **25-1** (0.5g, 4.0mmol) in anhydrous THF (15ml) in a dried flask was added NaH (0.1g, 4.8mmol) in portions. Once bubbling had subsided iodopropane (0.8ml, 8.0mmol) was added and stirred at room temperature overnight. To the reaction mixture was added another 0.5eq of NaH was added along with 3eq of iodopropane. After stirring for 50h another 0.5eq of NaH was added along with 2eq of iodopropane. The reaction mixture stirred for another 20h before being quenched with ethanol (5ml). Solvent removal afforded the desired product **25-2** as a solid.
MS calculated M+H: 169.2, found 155.1 ($M-CH_2$).

1-Propyl-1H-imidazole-4-carboxylic acid (**25-3**)

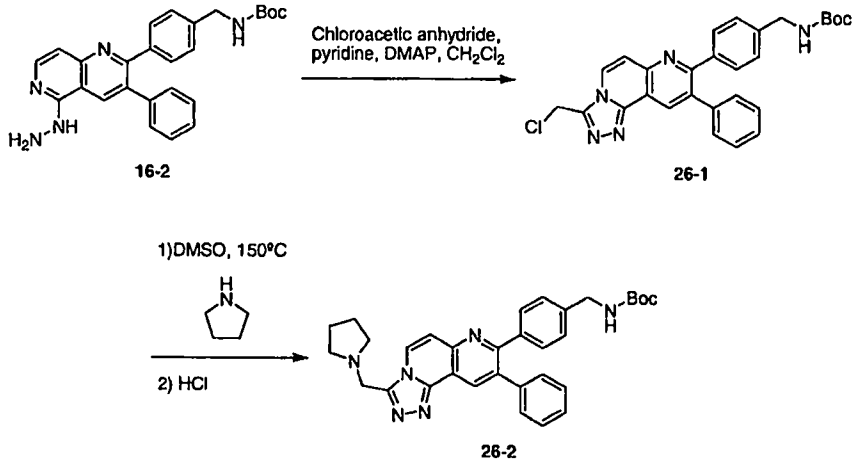
To a solution of **25-2** (0.6g, 3.6mmol) in anhydrous MeOH (2ml) was added 3N LiOH (2.6ml, 7.9mmol). The reaction mixture was heated at 80°C for 1h. The heat was reduced and the mixture was stirred at 40°C overnight. The reaction was then neutralized with 12N HCl and subsequently concentrated in vacuo. The residue was dried azeotropically with toluene to afford the desired product **25-3** as a solid. MS calculated M+H: 155.2, found 155.1

The following table (Table 9) contains compounds made using the procedures of Scheme 25 substituting the appropriate alkyl halide.

Table 9

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **25-4** |  | 1-isopropyl-1H-imidazole-4-carboxylic acid | 155.1 |
| **25-5** |  | 1-butyl-1H-imidazole-4-carboxylic acid | 155.1 |

SCHEME 26




4-[9-Phenyl-3-(pyrrolidin-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (**26-2**)

tert-Butyl 4-[3-(chloromethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylcarbamate (**26-1**)

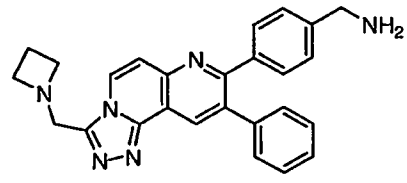
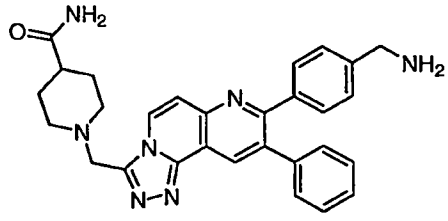
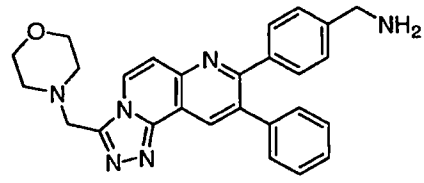
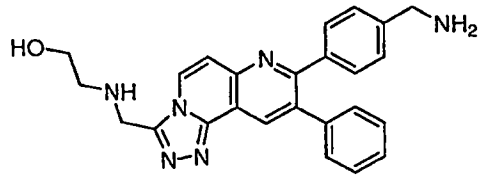
To a suspension of **16-2** (1.2g, 2.7mmol) in $CH_2Cl_2$ (10ml) was added DMAP (0.03g, 0.03mmol) and pyridine (0.4ml, 5.4mmol) followed by chloroacetic anhydride (0.5g, 3.0mmol). The reaction mixture was stirred at room temperature for 2h before adding additional chloroacetic anhydride (0.2g, 0.9mmol). After stirring for an additional 10min the solvent was removed in vacuo. The residue was partitioned between saturated aqueous $NaHCO_3$ and EtOAc (3x30ml). The combined organic layers were washed with water, brine and dried ($Na_2SO_4$/$MgSO_4$). Removal of the solvent afforded the desired product **26-1** as a red powder. MS calculated: 500.2, found 500.1

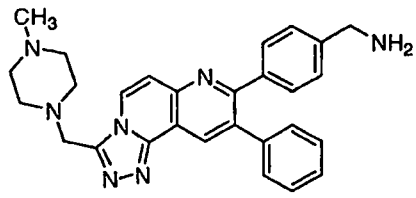
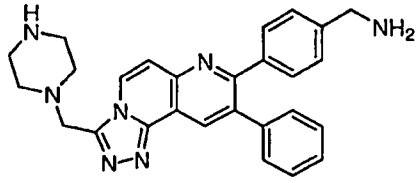
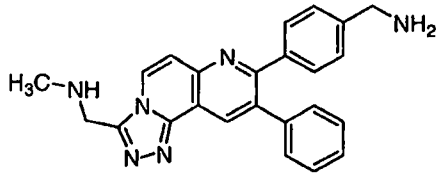
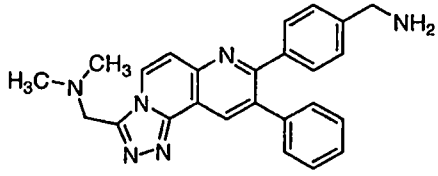
4-[9-Phenyl-3-(pyrrolidin-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine (26-2)

To a solution of **26-1** (0.05g, 0.1mmol) in DMSO (1ml) was added pyrrolidine. The solution was heated at 150°C for 30min. The reaction mixture was purified using reverse phase HPLC. The residue was dissolved in MeOH (0.5ml) and was treated with 1N HCl (0.4ml). The reaction mixture was stirred at 35°C for 1day. Solvent removal afforded the desired product **26-2** as a solid.
MS calculated: 535.7, 435.5

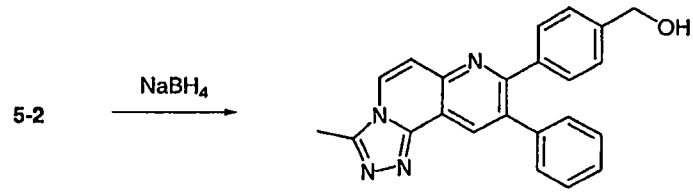
The following table (Table 10) contains compounds prepared using the procedures of Scheme 26 substituting the appropriate amine for pyrrolidine. The compounds in Table 10 were isolated as HCl salts.

Table 10

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **26-3** |  | 1-{4-[3-(azetidin-1-ylmethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | 421.2124 |
| **26-4** |  | 1-({8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methyl)piperidine-4-carboxamide | 492.249 |
| **26-5** |  | 1-{4-[3-(morpholin-4-ylmethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine | 451.2228 |
| **26-6** |  | 2-[({8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methyl)amino]ethanol | 425.2071 |

| | | | |
|---|---|---|---|
| 26-7 |  | 1-(4-{3-[(4-methyl piperazin-1-yl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine | 464.2543 |
| 26-8 |  | 4-[9-phenyl-3-(piperazin-1-ylmethyl)[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzylamine | 450.2386 |
| 26-9 |  | N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N-methylamine | 395.1969 |
| 26-10 |  | N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N,N-dimethylamine | 409.2125 |

SCHEME 28

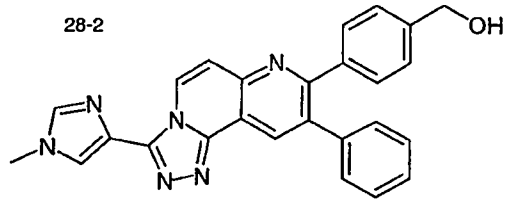



[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] methanol (28-1)

To a solution of 4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzaldehyde (5-2, 0.317 g, 0.870 mmol) in methanol (5 mL) was added sodium borohydride (0.033 g, 0.870 mmol) at 0°C. After 10 minutes, the reaction mixture was poured into ethyl acetate, and the organic layer was washed with a saturated solution of sodium bicarbonate, water, then brine, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure. Purification by reverse

phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water) gave the title compounds as a solid. HRMS ($M+H^+$): calculated = 367.1554, observed = 367.1547.

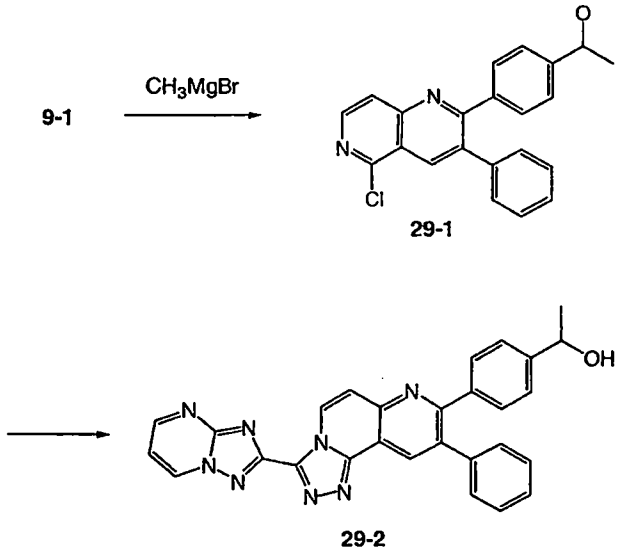
28-2



{4-[3-(1-Methyl-1*H*-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}methanol (**28-2**)

The title compound was prepared from **13-2** according to the procedure of Scheme 28; HRMS ($M+H^+$): calculated = 433.1772, observed = 433.1761.

SCHEME 29




1-[4-(9-Phenyl-3-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanol (**29-2**)

1-[4-(5-Chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethanol (**29-1**)

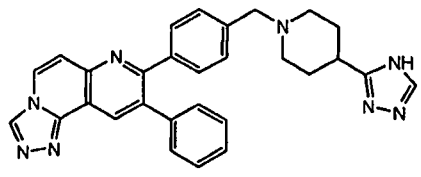
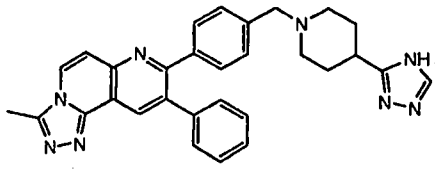
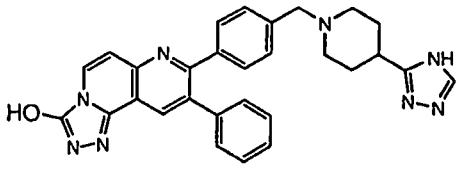
To a solution of 4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzaldehyde (**9-1**, 0.500 g, 1.450 mmol) in anhydrous methylene chloride (10 mL) was added methymagnesium bromide (2.072 mL, 2.9 mmol, 1.4M in toluene/tetrahydrofuran (75:25)) at 0°C. After 15 minutes, the reaction mixture was poured into ethyl acetate, and the organic layer was washed with a saturated solution of sodium bicarbonate, water, then brine, dried over sodium sulfate, filtered and concentrated to dryness under reduced pressure gave the title compound. MS ($M+H^+$): calculated = 361.85, observed = 361.1.

1-[4-(9-Phenyl-3-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanol (**29-2**)

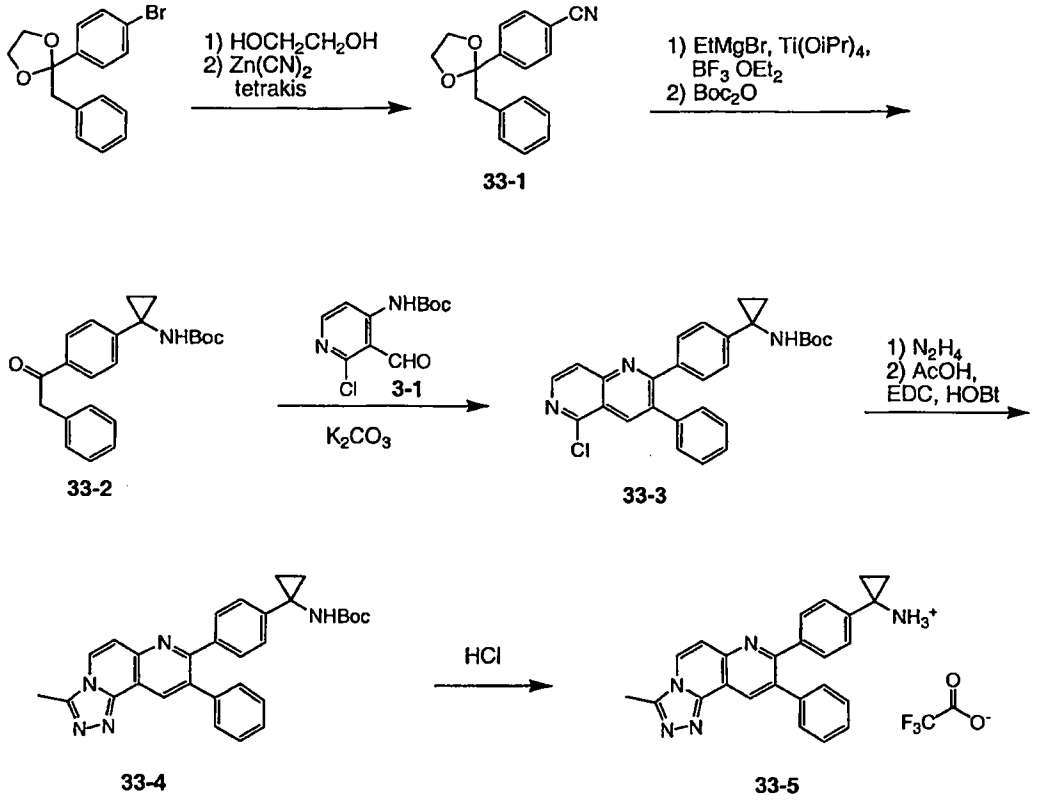
The title compound was prepared according to the procedures of Scheme 9; HRMS ($M+H^+$): calculated = 485.1833, observed = 485.1812.

The following compounds in Table 11 were prepared according to the procedure of Scheme 13 from piperidine **21-1** and the indicated aldehyde.

Table 11

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **30-1** **(from 4-2)** |  | 9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3, 4-*f*]-1,6-naphthyridine | Calc'd: 487.2353 Observed: 484.2371 |
| **31-1** **(from 5-2)** |  | 3-methyl-9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl] methyl} phenyl)[1,2,4]triazolo[3, 4-*f*]-1,6-naphthyridine; isolated as a HCl salt | Calc'd: 501.2510 Observed: 501.2531 |
| **32-1** **(from 3-6)** |  | 9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3, 4-*f*]-1,6-naphthyridin-3-ol | Calc'd: 503.2303 Observed: 503.2327 |

SCHEME 33




1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] cyclopropanaminium trifluoroacetate (**33-5**)

4-(2-Benzyl-1,3-dioxolan-2-yl)benzonitrile (**33-1**)

A solution of 1-(4-bromophenyl)-2-phenylethanone (5.0 g, 18 mmol), ethylene glycol (3.0 mL, 54 mmol) and tosic acid (0.04 g, 0.2 mmol) in toluene (30 mL) was heated to reflux with a Dean-Stark trap for 15 hours. The reaction was cooled to room temperature, diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated to give crude 2-benzyl-2-(4-bromophenyl)-1,3-dioxolane as a white solid. To the crude material was added zinc cyanide (2.3 g, 20 mmol), tetrakis(triphenylphosphine)palladium (3.3 g, 2.8 mmol), DMF (20 mL) and dioxane (20 mL) and the resulting suspension was purged with nitrogen for 15 minutes prior to being heated 100°C for 15 hours. The reaction was cooled to room temperature, poured into ether and filtered. The organic filtrate was washed with water, saturated bicarbonate, brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% ethyl acetate/ hexane → 50% ethyl acetate/ hexane) gave the title compound as white solid. MS ($M+H^+$): calculated = 265.31, observed = 266.1.

*tert*-Butyl {1-[4-(phenylacetyl)phenyl]cyclopropyl}carbamate (**33-2**)

To a solution of 4-(2-benzyl-1,3-dioxolan-2-yl)benzonitrile (**33-1**, 1.5 g, 5.6 mmol) in ether (25 mL) was added titanium isopropoxide (1.8 mL, 6.2 mmol) followed by ethyl magnesium

bromide (4.2 mL, 12 mmol, 3M in ether) at -78°C. After 10 minutes, the reaction was warmed to room temperature for 60 minutes. The reaction was cooled to 0°C and boron trifluoride etherate complex (1.4 mL, 11 mmol) was added. After 30 minutes at 0°C, the reaction was warmed to room temperature for 1 hour at which time the reaction was quenched and acidified with 1M HCl. The suspension was stirred for an additional 3 hours at room temperature, at which time the mixture was basified with 1M NaOH and extracted with chloroform. The combined organics were dried over sodium sulfate, filtered and concentrated. To the crude material was immediately added acetonitrile (15 mL) and di-tert-butyl dicarbonate (1.2 g, 5.6 mmol) at room temperature. After 12 hours, the reaction was concentrated to dryness and purified by silica gel chromatography (1% ethyl acetate/ hexane → 60% ethyl acetate/ hexane) to give the title compound as white solid. MS ($M+H^+$): calculated = 351.44, observed = 352.1.

*tert*-Butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]cyclopropyl}carbamate (33-3)

A solution of **33-2** (0.64 g, 2.5 mmol), 3-1 (0.88 g, 2.5 mmol) and potassium carbonate (2.1 g, 15 mmol) in DMF (14 mL) was heated to 120 °C for 4.5 hours. The reaction was cooled to room temperature, diluted with ethyl acetate, washed with water, brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% ethyl acetate/ hexane → 70% ethyl acetate/ hexane) gave the title compound as a foam. MS ($M+H^+$): calculated = 471.98, observed = 472.1.

*tert*-Butyl {1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropyl}carbamate (33-4)

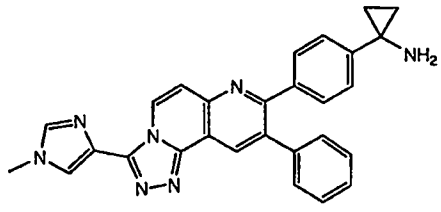
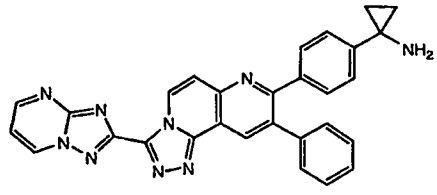
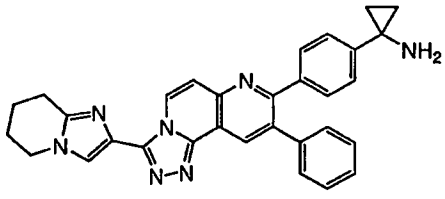
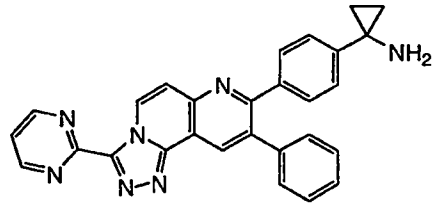
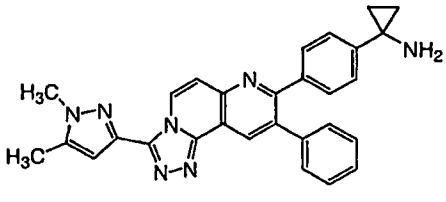
The title compound was prepared from 33-3 according to the procedure of Scheme 27; MS ($M+H^+$): calculated = 491.58, observed = 492.1.

1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] cyclopropanaminium trifluoroacetate (33-5)

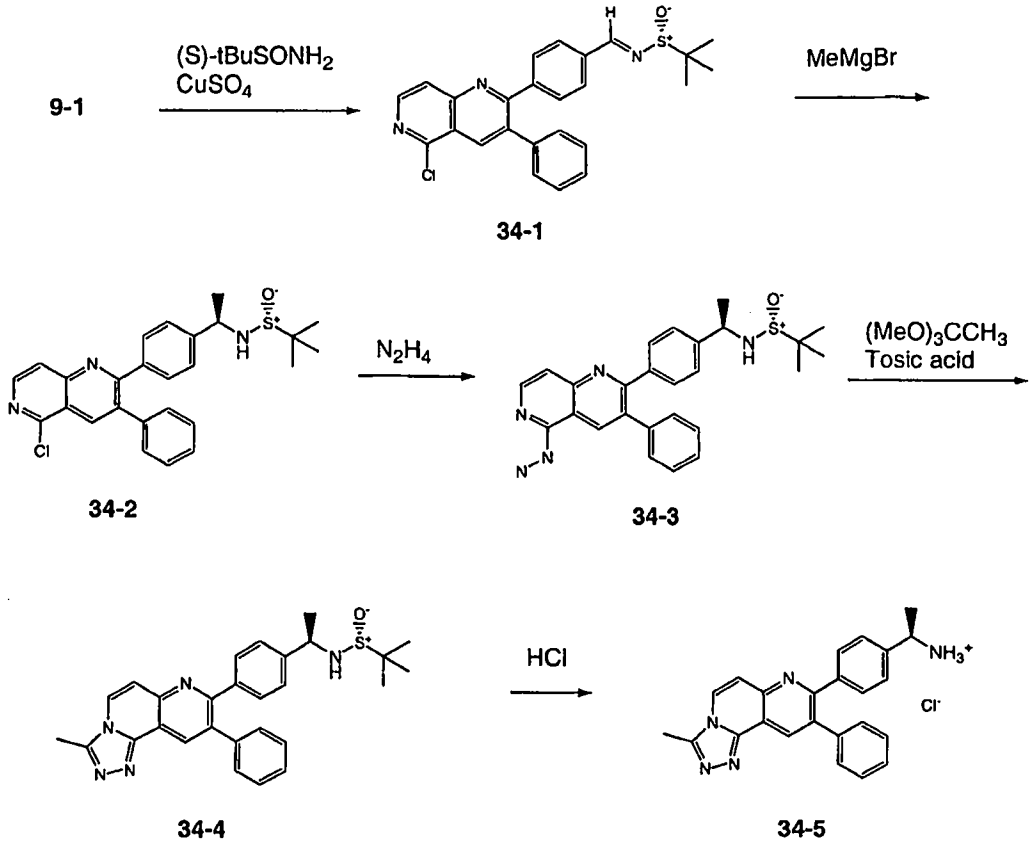
The title compound was prepared according to the procedure of Scheme 27; HRMS ($M+H^+$): calculated = 392.1870, observed = 392.1893.

The following compounds in Table 12 were prepared according to the procedure of Scheme 33. Compounds **33-8 – 33-10** were isolated as HCl salts. Compound **33-6** was isolated as a TFA salt.

Table 12

| Cmp | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **33-6** |  | 1-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl] phenyl}cyclo propanamine | Calc'd: 458.2088 Observed: 458.2114 |
| **33-7** |  | 1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-*a*] pyrimidin-2-yl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] cyclopropanamine | Calc'd: 496.1993 Observed: 496.1987 |
| **33-8** |  | 1-{4-[9-phenyl-3-(5,6,7,8-tetrahydro imidazo[1,2-a]pyridin-2-yl)[1,2,4] triazolo [3,4-f]-1,6-naphthyridin -8-yl] phenyl}cyclo propanamine | 498.238 |
| **33-9** |  | 1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]cyclopropanam ine | 456.1915 |
| **33-10** |  | 1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}cyclopropanam ine | 472.2227 |

SCHEME 34




(1R)-1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl ] ethanaminium chloride (34-5)

*N*-{(1*E*)-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methylene}-2-methylpropane-2-sulfinamide (34-1)

A solution of 4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)benzaldehyde (**9-1**, 4.24 g, 12.3 mmol), S-(-)-2-methylpropane-2-sulfinamide (3.43 mL, 28.3 mmol) and cupric sulfate (4.49 g, 28.1 mmol) in methylene chloride (20 mL) was heated to reflux under an atmosphere of nitrogen. After 18 hours, the reaction was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (0% ethyl acetate/ hexane → 45% ethyl acetate/ hexane) gave the title compound as an orange foam. MS ($M+H^+$): calculated = 447.99, observed = 448.2

*N*-{(1*R*)-1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}-2-methylpropane-2-sulfinamide (34-2)

To a solution of *N*-{(1*E*)-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]methylene}-2-methylpropane-2-sulfinamide (**34-1**, 4.53 g, 10.1 mmol) in methylene chloride (100 mL) was added methyl magnesium bromide (30 mL, 42.0 mmol, 1.4M in 75:25 toluene:THF) at -

10°C. After 30 minutes, the reaction was quenched by addition of saturated ammonium chloride solution (while maintaining the temperature below 0°C) and extracted with methylene chloride. The combined organics were washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give the title compound as a pale yellow solid. MS ($M+H^+$): calculated = 464.03, observed = 464.2

*tert*-Butyl({(1*R*)-1-[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl} amino)sulfoniumolate (**34-3**)

To a solution of a *N*-{(1*R*)-1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}-2-methylpropane-2-sulfinamide (**34-2**, 0.707 g, 1.52 mmol) and anhydrous hydrazine (15 ml) was heated at 115°C for 1 hour. The reaction mixture was poured into ethyl acetate, and the organic layer was washed with a saturated solution of sodium bicarbonate, then water, then brine, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure to give the crude hydrazine adduct as an orange solid. MS ($M+H^+$): calculated = 459.62, observed = 460.4.

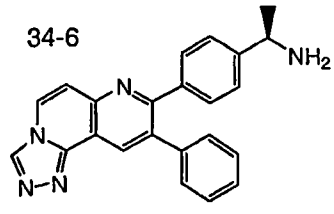
*tert*-Butyl({(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl}amino)sulfoniumolate (**34-4**)

To crude *tert*-butyl({(1*R*)-1-[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}amino)sulfoniumolate (**34-3**, 1.06g, 2.31mmol), p-toluenesulfonic acid (63mg, 0.36mmol), and trimethyl orthoacetate (1.0mL, 7.7mmol) was added anhydrous toluene (10mL) and heated to 110°C for 48 hours. The reaction mixture was reduced under pressure and purified by silica gel chromatography (0-10%methanol/methylene chloride) to give an orange foam. MS ($M+H^+$): calculated = 483.64, observed = 484.2.

(1R)-1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl] ethanaminium chloride (**34-5**)

*tert*-Butyl({(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}amino)sulfoniumolate (**34-4**) was treated with 4N HCl in dioxane at room temperature for 15 minutes. The reaction mixture was reduced under pressure and purified by reverse phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water) & conversion to HCl salt (addition of saturated solution of HCl in ethyl acetate (~ 4N) & concentration) gave the title compound as a solid. MS ($M+H^+$): calculated = 379.47, observed = 380.2.

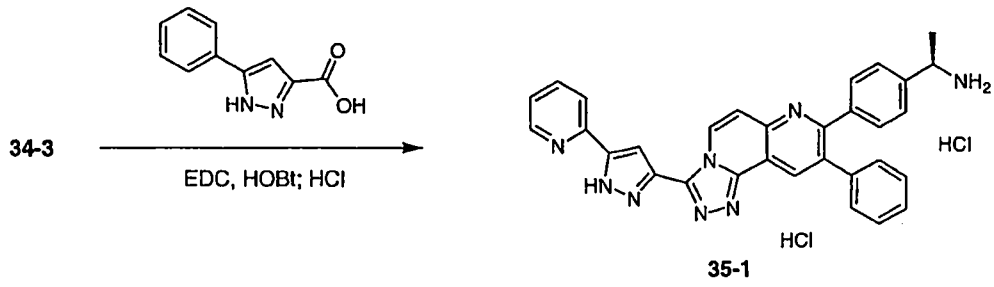
34-6




(1*R*)-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] ethanamine (**34-6**)

The title compound was prepared according the procedures of Scheme 34; MS ($M+H^+$): calculated = 365.43, observed = 366.2. Compound **34-6** was isolated as an HCl salt.

SCHEME 35



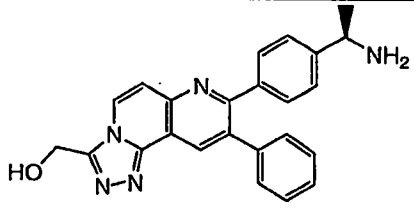
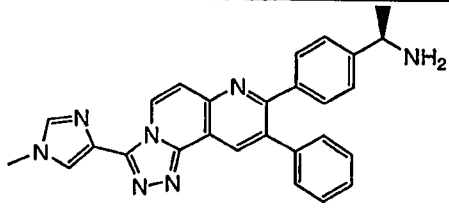

35-1

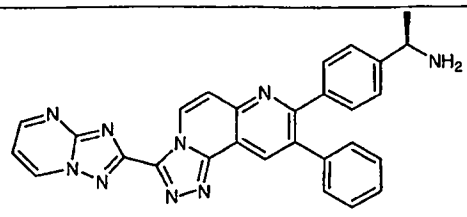
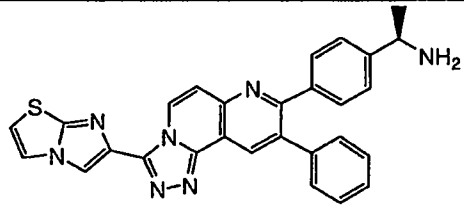
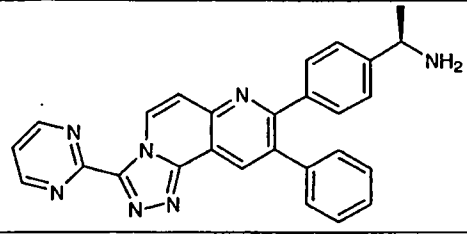
(1*R*)-1-{4-[9-Phenyl-3-(5-pyridin-2-yl-1*H*-pyrazol-3-yl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}ethanamine dihydrochloride (**35-1**)

To *tert*-butyl({(1*R*)-1-[4-(5-hydrazino-3-phenyl-1,6-naphthyridin-2-yl)phenyl]ethyl}amino)sulfoniumolate (**34-3**, 0.20 g, 0.43 mmol), EDC (0.11 g, 0.57 mmol), anhydrous HOBT (0.06 g, 0.39 mmol), DIPEA (0.17 mL, 0.96 mmol), and 5-pyridin-2-yl-1H-pyrazole-3-carboxylic acid (0.08g, 0.43 mmol) was added anhydrous DMF (2 mL) and stirred at room temperature overnight. HCl/Ether (1mL, 2N) was added to the reaction mixture and stirred for 20 min at room temperature, then microwaved at 100°C for 30min. The solvent was removed under vacuum and purified by reverse phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water) & conversion to HCl salt (addition of saturated solution of HCl in ethyl acetate (~ 4N) & concentration) gave the title compound as a solid. MS ($M+H^+$): calculated = 508.58, observed = 509.1.

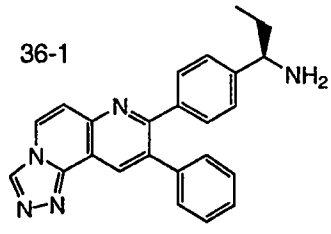
The following compounds in Table 13 were prepared according to the procedure of Scheme 35. The compounds in Table 13 were isolated as HCl salts.

Table 13

| Cmp | Structure | Name | MS m/z (M+H) |
|---|---|---|---|
| **35-2** |  | (1R)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine | Observed: 396.0 |
| **35-3** |  | (1R)-1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine | Observed: 445.9 |

| | | | |
|---|---|---|---|
| **35-4** |  | (1R)-1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine | Observed: 484.1 |
| **35-5** |  | (1R)-1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine | Observed: 488.0 |
| **35-6** |  | (1R)-1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine | Observed: 444.1 |

36-1

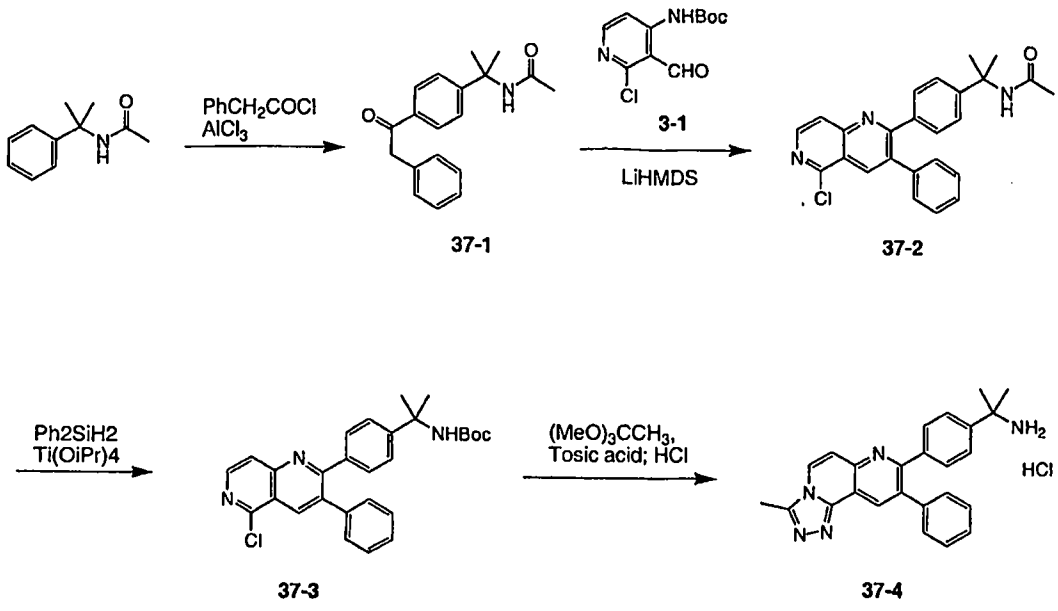


(1*R*)-1-[4-(9-Phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] propan-1-amine (**36-1**)

The title compound was prepared according the procedures of Scheme 34. MS ($M+H^+$): calculated = 379.47, observed = 380.2 Compound **36-1** was isolated as an HCl salt.

110

SCHEME 37




2-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine (37-4)

*N*-{1-methyl-1-[4-(phenylacetyl)phenyl]ethyl}acetamide (37-1)

A solution of *N*-(1-methyl-1-phenylethyl)acetamide (21.3 g, 121 mmol), phenylacetyl chloride (19.5 g, 126 mmol) and aluminum trichloride (19 g, 142 mmol) in methylene chloride (140 mL) was stirred overnight at room temperature under an atmosphere of nitrogen. The reaction was poured onto ice and stirred until the ice melted, then the layers were separated and the organic layer was washed with saturated sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography gave the title compound. MS ($M+H^+$): calculated = 295.38, observed = 296.1

*N*-{1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-1-methylethyl} acetamide (37-2)

The title compound was prepared from **37-1** according to the procedure of Scheme 3; MS ($M+H^+$): calculated = 415.91, observed = 416.1

*tert*-Butyl {1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-1-methylethyl} carbamate (37-3)

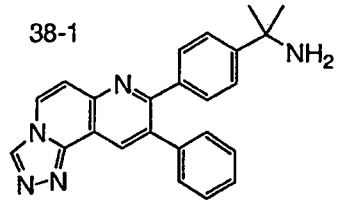
To a solution of *N*-{1-[4-(5-chloro-3-phenyl-1,6-naphthyridin-2-yl)phenyl]-1-methylethyl}acetamide (**37-2**, 4.73 g, 11.4 mmol) in anhydrous THF (120 mL) was added diphenylsilane (10.5 ml, 56.9 mmol) and titanium isopropoxide (16.6 mL, 56.9 mmol) at 40°C for 1 hour. The reaction mixture was removed from heat and quenched by addition of saturated bicarbonate solution. Methylene chloride was added and filtered through a pad of celite and magnesium sulfate. Di-tert-butyl dicarbonate (3.08g, 14.1mmol) was added to the solution before rotavaping to min volume. Anhydrous methylene

chloride (140mL), di-tert-butyl dicarbonate (4.1g, 18.8mmol), and TEA (4.0mL, 28.7mmol) were added and stirred overnight at room temperature. The reaction mixture was washed with sodium bicarbonate, brine, dried over magnesium sulfate, filtered, and concentrated. Purified by silica gel chromatography (0-40% EtOAc/hex over 30min) gave the title compound as a white foam. MS ($M+H^+$): calculated = 473.99, observed = 474.1

2-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine hydrochloride (**37-4**)

The title compound was prepared from **37-3** according to the procedures of Scheme 5; MS ($M+H^+$): calculated = 393.48, observed = 394.1.

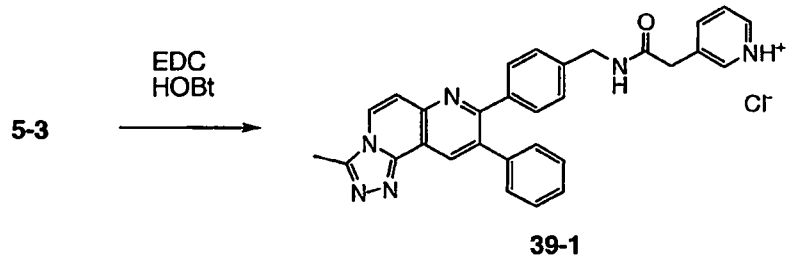
38-1



2-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] propan-2-amine (**38-1**)

The title compound was prepared according to the procedures of Scheme 37; MS ($M+H^+$): calculated = 421.51, observed = 422.3. Compound **38-1** was isolated as an HCl salt.

SCHEME 39




**39-1**

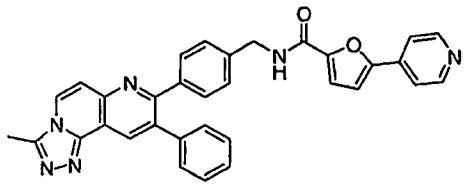
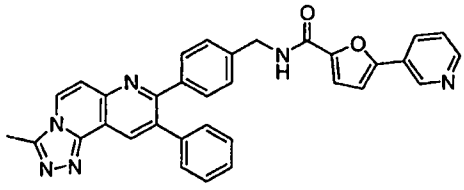
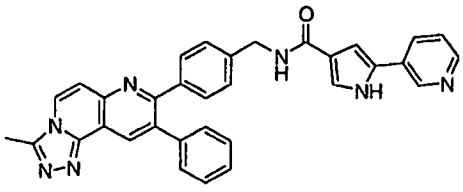
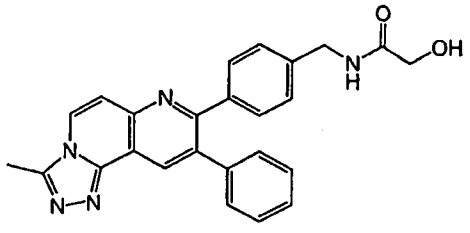
3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridinium chloride (**39-1**)

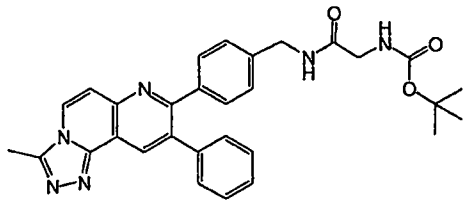
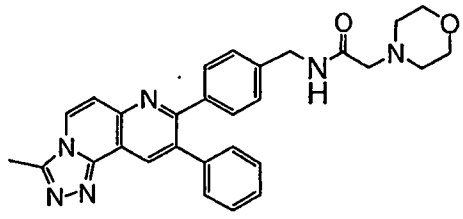
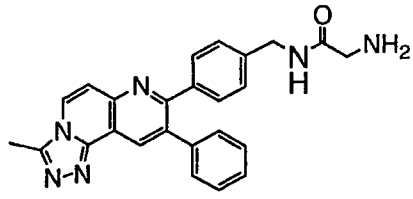
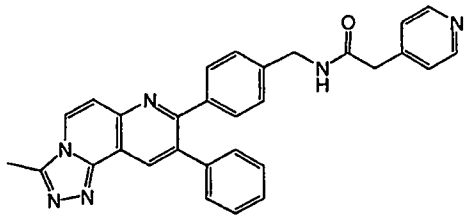
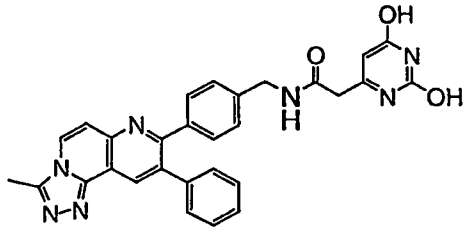
To 1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]methanamine hydrochloride (**5-3**, 20 mg, 0.050 mmol) ), EDC (12 mg, 0.065 mmol), HOBT (10 mg, 0.0650 mmol), DIPEA (0.033 ml, 0.199 mmol), and pyridin-3-ylacetic acid hydrochloride (11 mg, 0.0650 mmol) was added 0.6 mL anhydrous dimethylformamide. The reaction mixture was then heated under microwave irradiation at 100°C for 5 minutes. Purification of crude reaction mixture by reverse phase chromatography (Waters Sunfire MSC18, 1% acetonitrile / 0.1% trifluoroacetic acid / water → 95% acetonitrile / 0.1% trifluoroacetic acid / water) & conversion to HCl salt (addition of

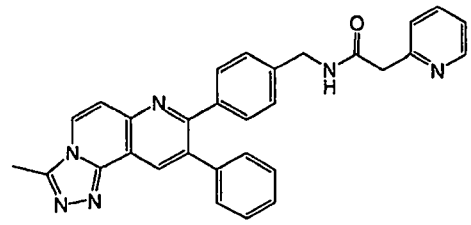
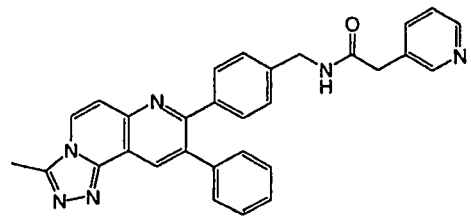
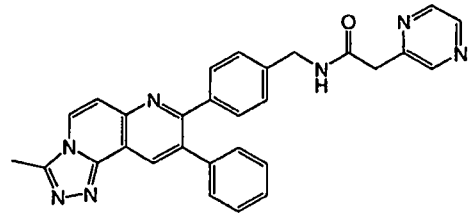
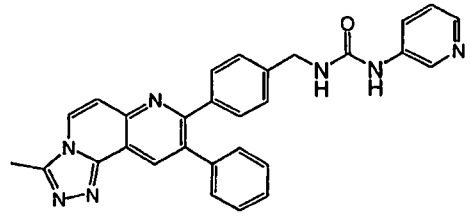
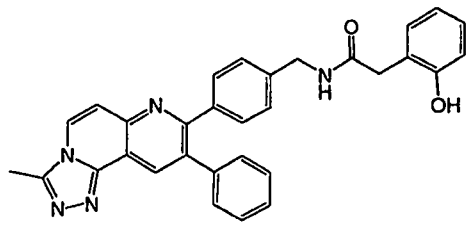
saturated solution of HCl in ethyl acetate (~ 4N) & concentration) gave the title compound as yellow solid. HRMS ($M+H^+$): calculated = 243.1079, observed = 243.1083.

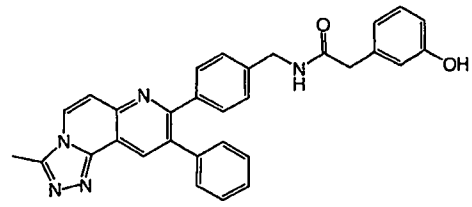
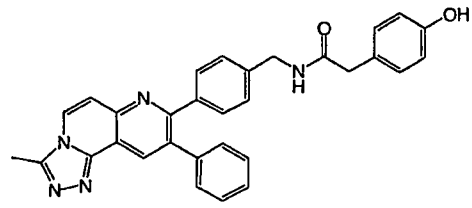
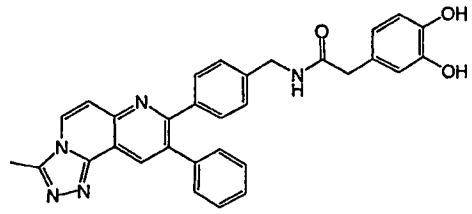
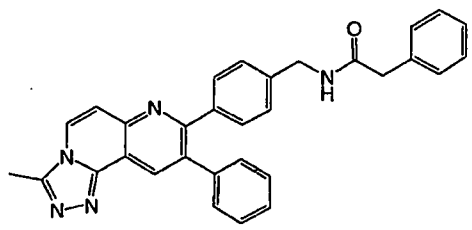
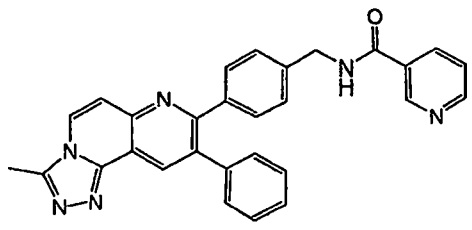
The following compounds in Table 14 were prepared from the indicated amine (see the Cmp column parentheticals) according to the procedure of Scheme 39.

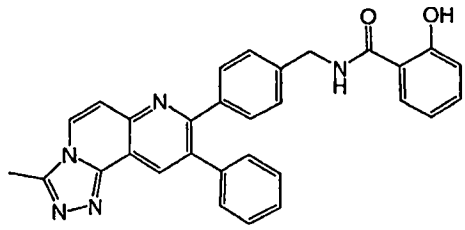
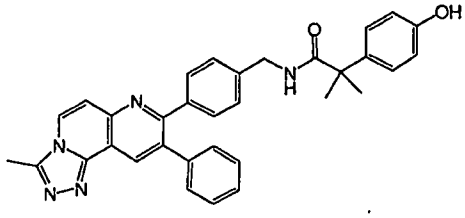
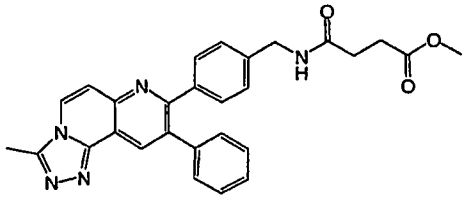
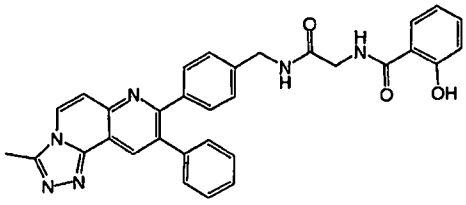
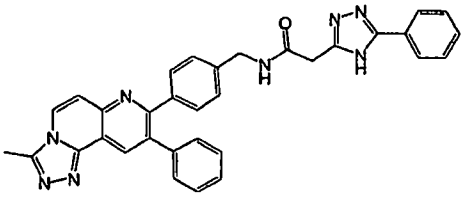
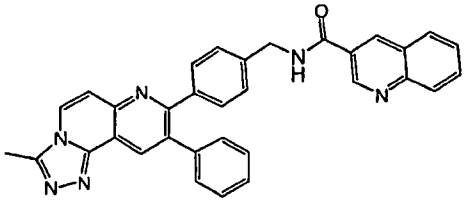
Table 14

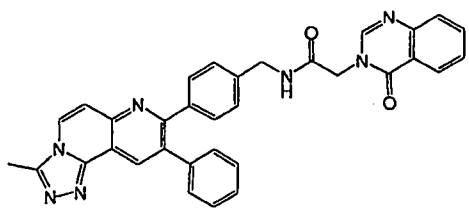
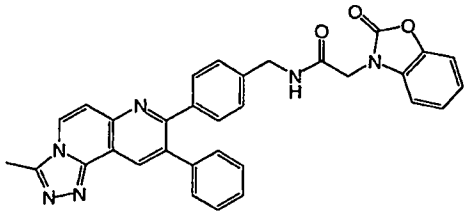
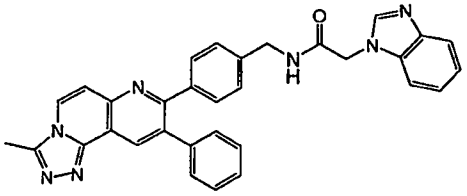
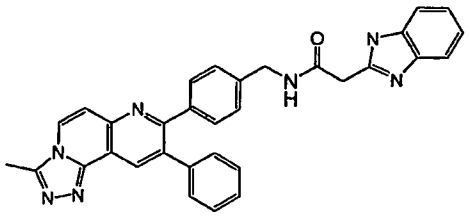
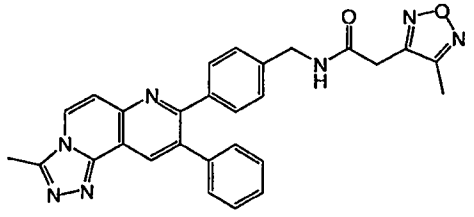
| Cmp (amine) | Structure | Name | HRMS m/z (M+H) |
|---|---|---|---|
| **39-2** **(5-3)** |  | *N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-4-yl-2-furamide; isolated as a TFA salt | Calc'd: 537.2034 Observed: 537.2027 |
| **39-3** **(5-3)** |  | *N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-2-furamide; isolated as a HCl salt | Calc'd: 537.2034 Observed: 537.2023 |
| **39-4** **(5-3)** |  | *N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-1*H*-pyrrole-3-carboxamide; isolated as a HCl salt | Calc'd: 536.2194 Observed: 536.2218 |
| **39-5** **(5-3)** |  | 2-hydroxy-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide | Calc'd: 424.1768 Observed: 424.1767 |

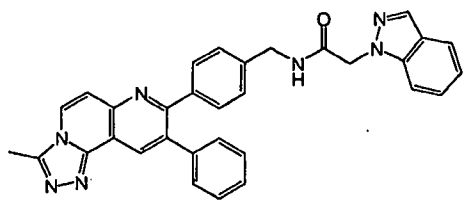
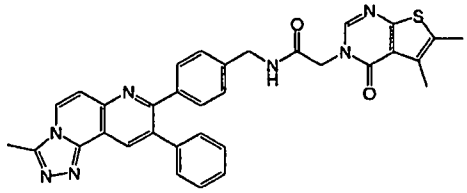
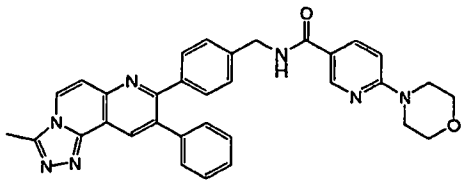
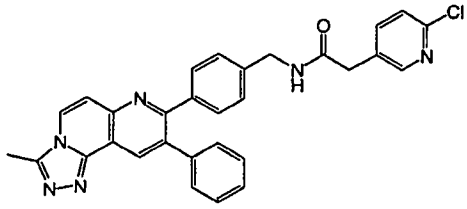
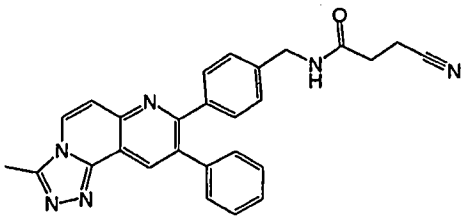
| | | | |
|---|---|---|---|
| **39-6**<br><br>**(5-3)** |  | *tert*-butyl (2-{[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]amino}-2-oxoethyl)carbamate | Calc'd: 523.2452<br>Observed: 523.2444 |
| **39-7**<br><br>**(5-3)** |  | 4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)morpholine; isolated as an HCl salt | Calc'd: 493.2347<br>Observed: 493.2358 |
| **39-8**<br><br>**(5-3)** |  | 2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethanamine; isolated as an HCl salt | Calc'd: 423.1928<br>Observed: 423.1942 |
| **39-9**<br><br>**(5-3)** |  | 4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine; isolated as an HCl salt | Calc'd: 485.2085<br>Observed: 485.2120 |
| **39-10**<br><br>**(5-3)** |  | 2,4-dihydroxy-6-(2-{[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyrimidine; isolated as an HCl salt | Calc'd: 518.1935<br>Observed: 518.1960 |

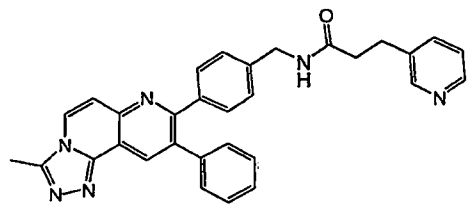
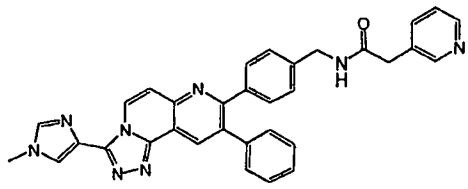
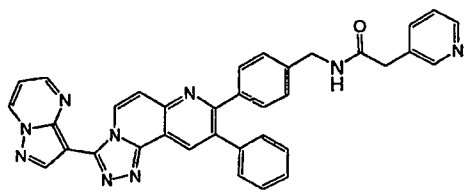
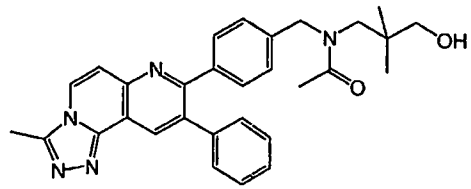
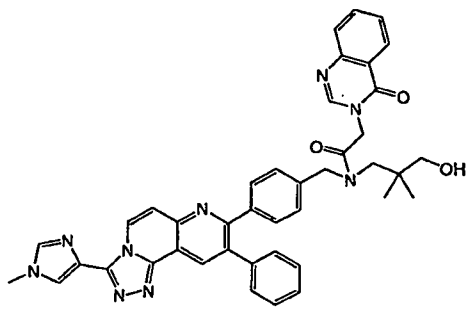
| | | | |
|---|---|---|---|
| **39-11**<br><br>**(5-3)** |  | 2-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine; isolated as an HCl salt | Calc'd: 485.2085<br>Observed: 485.2118 |
| **39-12**<br><br>**(5-3)** |  | 3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridinium chloride | Calc'd: 243.1079<br>Observed: 243.1083 |
| **39-13**<br><br>**(5-3)** |  | *N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-pyrazin-2-ylacetamide | Calc'd: 486.2037<br>Observed: 486.2044 |
| **39-14**<br><br>**(5-3)** |  | 3-methyl-9-phenyl-8-[4-({[(pyridin-3-ylamino)carbonyl]amino}methyl)phenyl][1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 486.2037<br>Observed: 486.2056 |
| **39-15**<br><br>**(5-3)** |  | 2-(2-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide | Calc'd: 500.2081<br>Observed: 500.2087 |

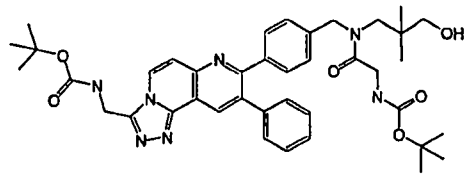
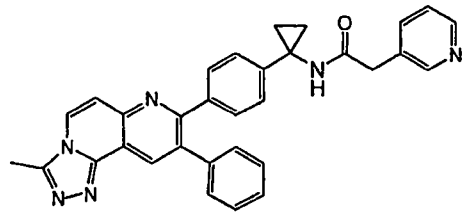
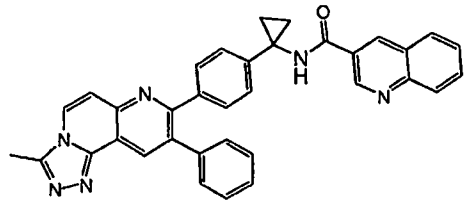
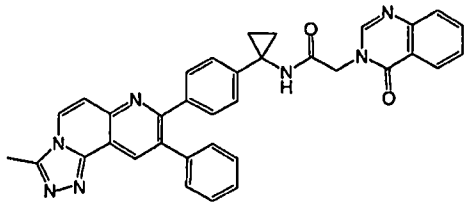
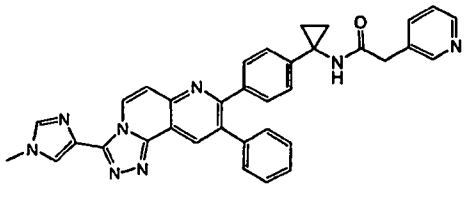
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|---|---|---|---|
| **39-16**<br>**(5-3)** |  | 2-(3-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide | Calc'd: 500.2081<br>Observed: 500.2086 |
| **39-17**<br>**(5-3)** |  | 2-(4-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide | Calc'd: 500.2081<br>Observed: 500.2085 |
| **39-18**<br>**(5-3)** |  | 2-(3,4-dihydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide | Calc'd: 576.2030<br>Observed: 576.2025 |
| **39-19**<br>**(5-3)** |  | *N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl] -2-phenylacetamide | Calc'd: 484.2132<br>Observed: 484.2161 |
| **39-20**<br>**(5-3)** |  | 3-methyl-9-phenyl-8-(4-{[(pyridin-3-ylcarbonyl) amino]methyl}phenyl)[1, 2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 471.1928<br>Observed: 471.1928 |

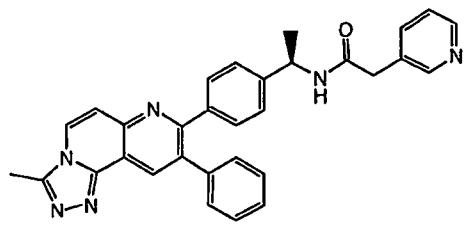
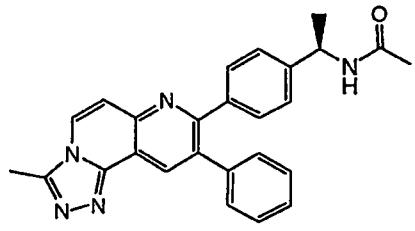
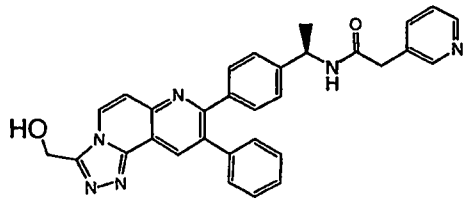
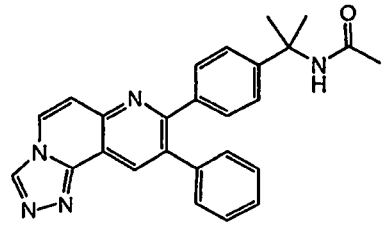
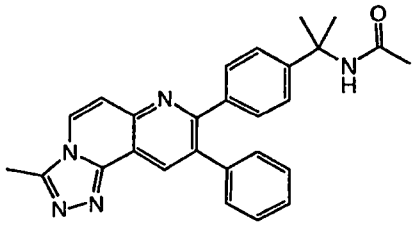
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| **39-21**<br>**(5-3)** |  | 2-hydroxy-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]benzamide | Calc'd: 486.1925<br>Observed: 486.1919 |
| **39-22**<br>**(5-3)** |  | 2-(4-hydroxyphenyl)-2-methyl-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]propanamide | Calc'd: 528.2394<br>Observed: 528.2386 |
| **39-23**<br>**(5-3)** |  | methyl 4-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-4-oxobutanoate | Calc'd: 480.2030<br>Observed: 480.2030 |
| **39-24**<br>**(5-3)** |  | 2-hydroxy-*N*-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)benzamide | Calc'd: 543.2139<br>Observed: 543.2127 |
| **39-25**<br>**(5-3)** |  | *N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetamide | Calc'd: 551.2303<br>Observed: 551.2292 |
| **39-26**<br>**(5-3)** |  | 3-methyl-9-phenyl-8-(4-{[(quinolin-3-ylcarbonyl)amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 521.2085<br>Observed: 521.2061 |

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| **39-27**<br>**(5-3)** |  | *N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide | Calc'd: 552.2143<br>Observed: 552.2126 |
| **39-28**<br>**(5-3)** |  | *N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetamide | Calc'd: 541.1983<br>Observed: 541.1965 |
| **39-29**<br>**(5-3)** |  | 8-(4-{[(1*H*-benzimidazol-1-ylacetyl)amino]methyl}phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 524.2194<br>Observed: 524.2199 |
| **39-30**<br>**(5-3)** |  | 8-(4-{[(1*H*-benzimidazol-2-ylacetyl)amino]methyl}phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 524.2194<br>Observed: 524.2185 |
| **39-31**<br>**(5-3)** |  | 2-(4-methyl-1,2,5-oxadiazol-3-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide | Calc'd: 440.1986<br>Observed: 490.1976 |

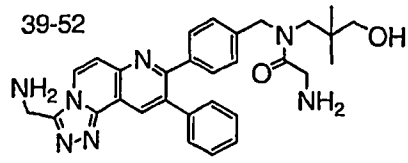
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| **39-32**<br>**(5-3)** |  | 2-(1*H*-indazol-1-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide | Calc'd: 524.2194<br>Observed: 524.2171 |
| **39-33**<br>**(5-3)** |  | 2-(5,6-dimethyl-4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide | Calc'd: 586.2020<br>Observed: 586.1993 |
| **39-34**<br>**(5-3)** |  | 3-methyl-8-[4-({[(6-morpholin-4-ylpyridin-3-yl)carbonyl]amino}methyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 556.2456<br>Observed: 556.2441 |
| **39-35**<br>**(5-3)** |  | 2-(6-chloropyridin-3-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide | Calc'd: 519.1695<br>Observed: 519.1673 |
| **39-36**<br>**(5-3)** |  | 3-cyano-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]propanamide | Calc'd: 447.1928<br>Observed: 447.1921 |

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| **39-37**<br><br>**(5-3)** |  | 3-methyl-9-phenyl-8-(4-{[(3-pyridin-3-yl propanoyl)amino]methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 499.2241<br>Observed: 499.2244 |
| **39-38**<br><br>**(16-44)** |  | 3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{[(pyridin-3-ylacetyl) amino]methyl}phenyl)[1, 2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 551.2303<br>Observed: 551.2326 |
| **39-39**<br><br>**(16-22)** |  | 9-phenyl-3-pyrazolo[1,5-*a*]pyrimidin-3-yl-8-(4-{[(pyridin-3-ylacetyl) amino]methyl}phenyl)[1, 2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as an HCl salt | Calc'd: 588.2255<br>Observed: 588.2276 |
| **39-40**<br><br>**(13-10)** |  | *N*-(3-hydroxy-2,2-dimethylpropyl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl ) benzyl]acetamide | Calc'd: 494.2551<br>Observed: 494.2557 |
| **39-41**<br><br>**(13-16)** |  | *N*-(3-hydroxy-2,2-dimethylpropyl)-*N*-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl ] benzyl}-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide | LRMS<br>(M+1)=<br>Observed: 704.3 |

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| **39-42**<br>**(13-20)** |  | *tert*-butyl {2-[[4-(3-{[(*tert*-butoxycarbonyl) amino]methyl}-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl](3-hydroxy-2,2-dimethylpropyl)amino]-2-oxoethyl}carbamate | Calc'd: 724.3817<br>Observed: 724.3822 |
| **39-43**<br>**(33-5)** |  | 3-methyl-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino]cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as a TFA salt | Calc'd: 511.2241<br>Observed: 511.2264 |
| **39-44**<br>**(33-5)** |  | 3-methyl-9-phenyl-8-(4-{1-[(quinolin-3-yl carbonyl) amino] cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as a TFA salt | Calc'd: 547.2241<br>Observed: 547.2225 |
| **39-45**<br>**(33-5)** |  | *N*-{1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropyl}-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide | Calc'd: 578.2299<br>Observed: 578.2276 |
| **39-46**<br>**(33-6)** |  | 3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino] cyclopropyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine; isolated as a TFA salt | Calc'd: 577.2459<br>Observed: 577.2488 |

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| **39-47**<br><br>**(34-5)** |  | *N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}-2-pyridin-3-ylacetamide; isolated as a HCl salt | LRMS<br>(M+1)=<br>Observed: 498.8 |
| **39-48**<br><br>**(34-5)** |  | *N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl} acetamide | LRMS<br>(M+1)=<br>Observed: 422.2 |
| **39-49**<br><br>**(34-5)** |  | *N*-((1*R*)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}ethyl)-2-pyridin-3-ylacetamide; isolated as a HCl salt | LRMS<br>(M+1)=<br>Observed: 514.8 |
| **39-50**<br><br>**(38)** |  | *N*-{1-methyl-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl}acetamide | LRMS<br>(M+1)=<br>Observed: 422.3 |
| **39-51**<br><br>**(37-4)** |  | *N*-{1-methyl-1-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl}acetamide | LRMS<br>(M+1)=<br>Observed: 435.8 |

39-52



2-[{4-[3-(ammoniomethyl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]benzyl}(3-hydroxy-2,2-dimethylpropyl)amino]-2-oxoethanamine (**39-52**)

The title compound was prepared according to the procedures of Scheme 27 from 39-42; MS (M+H$^+$): Calc'd: 524.2769, Observed: 524.2777. Compound **39-52** was isolated as an HCl salt.

## EXAMPLE 1

### Cloning of the human Akt isoforms and ΔPH-Akt1

The pS2neo vector (deposited in the ATCC on April 3, 2001 as ATCC PTA-3253) was prepared as follows: The pRmHA3 vector (prepared as described in *Nucl. Acid Res.* 16:1043-1061 (1988)) was cut with BglII and a 2734 bp fragment was isolated. The pUChsneo vector (prepared as described in *EMBO J.* 4:167-171 (1985)) was also cut with BglII and a 4029 bp band was isolated. These two isolated fragments were ligated together to generate a vector termed pS2neo-1. This plasmid contains a polylinker between a metallothionine promoter and an alcohol dehydrogenase poly A addition site. It also has a neo resistance gene driven by a heat shock promoter. The pS2neo-1 vector was cut with Psp5II and BsiWI. Two complementary oligonucleotides were synthesized and then annealed (CTGCGGCCGC (SEQ.ID.NO.: 1) and GTACGCGGCCGCAG (SEQ.ID.NO.: 2)). The cut pS2neo-1 and the annealed oligonucleotides were ligated together to generate a second vector, pS2neo. Added in this conversion was a NotI site to aid in the linearization prior to transfection into S2 cells.

Human Akt1 gene was amplified by PCR (Clontech) out of a human spleen cDNA (Clontech) using the 5' primer: 5'CGCGAATTCAGATCTACCATGAGCGACGTGGCTATTGTG 3' (SEQ.ID.NO.: 3), and the 3' primer: 5'CGCTCTAGAGGATCCTCAGGCCGTGCTGCTGGC3' (SEQ.ID.NO.: 4). The 5' primer included an EcoRI and BglII site. The 3' primer included an XbaI and BamHI site for cloning purposes. The resultant PCR product was subcloned into pGEM3Z (Promega) as an EcoRI/Xba I fragment. For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt1 gene using the PCR primer: 5'GTACGATGCTGAACGATATCTTCG 3' (SEQ.ID.NO.: 5). The resulting PCR product encompassed a 5' KpnI site and a 3' BamHI site which were used to subclone the fragment in frame with a biotin tag containing insect cell expression vector, pS2neo.

For the expression of a pleckstrin homology domain ( PH ) deleted (Δaa 4-129, which includes deletion of a portion of the Akt1 hinge region) version of Akt1, PCR deletion mutagenesis was done using the full length Akt1 gene in the pS2neo vector as template. The PCR was carried out in 2 steps using overlapping internal primers (5'GAATACATGCCGATGGAAAGCGACGGGGCTGAAGAGATGGAGGTG 3' (SEQ.ID.NO.: 6), and 5'CCCCTCCATCTCTTCAGCCCCGTCGCTTTCCATCGGCATG

TATTC 3' (SEQ.ID.NO.: 7)) which encompassed the deletion and 5' and 3' flanking primers which encompassed the KpnI site and middle T tag on the 5' end. The final PCR product was digested with KpnI and SmaI and ligated into the pS2neo full length Akt1 KpnI/SmaI cut vector, effectively replacing the 5' end of the clone with the deleted version.

Human Akt3 gene was amplified by PCR of adult brain cDNA (Clontech) using the amino terminal oligo primer:

5' GAATTCAGATCTACCATGAGCGATGTTACCATTGTG 3' (SEQ.ID.NO.: 8); and the carboxy terminal oligo primer :

5' TCTAGATCTTATTCTCGTCCACTTGCAGAG 3'(SEQ.ID.NO.: 9).

These primers included a 5' EcoRI/BglII site and a 3' XbaI/BglII site for cloning purposes. The resultant PCR product was cloned into the EcoRI and XbaI sites of pGEM4Z (Promega). For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt3 clone using the PCR primer:

5'GGTACCATGGAATACATGCCGATGGAAAGCGATGTTACCATTGTGAAG 3'(SEQ.ID.NO.: 10). The resultant PCR product encompassed a 5' KpnI site which allowed in frame cloning with the biotin tag containing insect cell expression vector, pS2neo.

Human Akt2 gene was amplified by PCR from human thymus cDNA (Clontech) using the amino terminal oligo primer:

5' AAGCTTAGATCTACCATGAATGAGGTGTCTGTC 3' (SEQ.ID.NO.: 11); and the carboxy terminal oligo primer: 5'GAATTCGGATCCTCACTCGCGGATGCTGGC 3' (SEQ.ID.NO.: 12). These primers included a 5' HindIII/BglII site and a 3' EcoRI/BamHI site for cloning purposes. The resultant PCR product was subcloned into the HindIII/EcoRI sites of pGem3Z (Promega). For expression/purification purposes, a middle T tag was added to the 5' end of the full length Akt2 using the PCR primer: 5'GGTACCATGGAATACATGCCGATGGAAAATGAGGTGTCTGTCATCAAAG 3' (SEQ.ID.NO.: 13). The resultant PCR product was subcloned into the pS2neo vector as described above.

## EXAMPLE 2

### Expression of human Akt isoforms and ΔPH-Akt1

The DNA containing the cloned Akt1, Akt2, Akt3 and ΔPH-Akt1 genes in the pS2neo expression vector was purified and used to transfect *Drosophila* S2 cells (ATCC) by the calcium phosphate method. Pools of antibiotic (G418, 500 μg/ml) resistant cells were selected. Cell were expanded to a 1.0 L volume (~7.0 x $10^6$ / ml), biotin and $CuSO_4$ were added to a final concentration of 50 μM and 50 mM respectively. Cells were grown for 72 h at 27°C and harvested by centrifugation. The cell paste was frozen at –70°C until needed.

## EXAMPLE 3

### Purification of human Akt isoforms and ΔPH-Akt1

Cell paste from one liter of S2 cells, described in Example 2, was lysed by sonication with 50 mls 1% CHAPS in buffer A: (50mM Tris pH 7.4, 1mM EDTA, 1mM EGTA, 0.2mM AEBSF,

10μg/ml benzamidine, 5μg/ml of leupeptin, aprotinin and pepstatin each, 10% glycerol and 1mM DTT). The soluble fraction was purified on a Protein G Sepharose fast flow (Pharmacia) column loaded with 9mg/ml anti-middle T monoclonal antibody and eluted with 75 μM EYMPME (SEQ.ID.NO.: 14) peptide in buffer A containing 25% glycerol. Akt/PKB containing fractions were pooled and the protein purity evaluated by SDS-PAGE. The purified protein was quantitated using a standard Bradford protocol. Purified protein was flash frozen on liquid nitrogen and stored at -70°C.

Akt and Akt pleckstrin homology domain deletions purified from S2 cells required activation. Akt and Akt pleckstrin homology domain deletions were activated (Alessi et al. *Current Biology* 7:261-269) in a reaction containing 10 nM PDK1 (Upstate Biotechnology, Inc.), lipid vesicles (10 μM phosphatidylinositol-3,4,5-trisphosphate – Metreya, Inc, 100 μM phosphatidylcholine and 100 μM phosphatidylserine – Avanti Polar lipids, Inc.) and activation buffer (50 mM Tris pH7.4, 1.0 mM DTT, 0.1 mM EGTA, 1.0 μM Microcystin–LR, 0.1 mM ATP, 10 mM $MgCl_2$, 333 μg/ml BSA and 0.1mM EDTA). The reaction was incubated at 22°C for 4 hours. Aliquots were flash frozen in liquid nitrogen.

## EXAMPLE 4

### Akt Kinase Assays

Activated Akt isoforms and pleckstrin homology domain deletion constructs were assayed utilizing a GSK-derived biotinylated peptide substrate. The extent of peptide phosphorylation was determined by Homogeneous Time Resolved Fluorescence (HTRF) using a lanthanide chelate(Lance)-coupled monoclonal antibody specific for the phosphopeptide in combination with a streptavidin-linked allophycocyanin (SA-APC) fluorophore which will bind to the biotin moiety on the peptide. When the Lance and APC are in proximity (i.e. bound to the same phosphopeptide molecule), a non-radiative energy transfer takes place from the Lance to the APC, followed by emission of light from APC at 665 nm.

Materials required for the assay:

A. Activated Akt isozyme or pleckstrin homology domain deleted construct

B. Akt peptide substrate: GSK3α (S21) Peptide #3928 biotin-GGRARTSSFAEPG (SEQ.ID.NO.:15), Macromolecular Resources.

C. Lance labeled anti-phospho GSK3α monoclonal antibody (Cell Signaling Technology, clone # 27).

D. SA-APC (Prozyme catalog no. PJ25S lot # 896067).

E. Microfluor®B U Bottom Microtiter Plates (Dynex Technologies, Catalog no. 7205).

F. Discovery® HTRF Microplate Analyzer, Packard Instrument Company.

G. 100 X Protease Inhibitor Cocktail (PIC): 1 mg/ml benzamidine, 0.5 mg/ml pepstatin, 0.5 mg/ml leupeptin, 0.5 mg/ml aprotinin.

H. 10X Assay Buffer: 500 mM HEPES, pH 7.5, 1% PEG, mM EDTA, 1 mM EGTA, 1% BSA, 20 mM θ-Glycerol phosphate.

I. Quench Buffer: 50 mM HEPES pH 7.3, 16.6 mM EDTA, 0.1% BSA, 0.1% Triton X-100, 0.17 nM Lance labeled monoclonal antibody clone # 27, 0.0067 mg/ml SA-APC

J. ATP/$MgCl_2$ working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 125 mM KCl, 5% Glycerol, 25 mM $MgCl_2$, 375 TM ATP

K. Enzyme working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, active Akt. The final enzyme concentrations were selected so that the assay was in a linear response range.

L. Peptide working solution: 1X Assay buffer, 1 mM DTT, 1X PIC, 5% Glycerol, 2 TM GSK3 biotinylated peptide # 3928

The reaction is assembled by adding 16 TL of the ATP/$MgCl_2$ working solution to the appropriate wells of a 96-well microtiter plate. Inhibitor or vehicle (1.0 Tl ) is added followed by 10 Tl of peptide working solution. The reaction is started by adding 13 Tl of the enzyme working solution and mixing. The reaction is allowed to proceed for 50 min and then stopped by the addition of 60 Tl HTRF quench buffer. The stopped reactions were incubated at room temperature for at least 30 min and then read on the Discovery instrument.

Procedure for Streptavidin Flash Plate Assay:

Step 1:

A 1 µl solution of the test compound in 100% DMSO was added to 20 µl of 2X substrate solution (20 uM GSK3 Peptide, 300 µM ATP, 20 mM $MgCl_2$, 20 µCi / ml [$\gamma^{33}$P] ATP, 1X Assay Buffer, 5% glycerol, 1 mM DTT, 1X PIC, 0.1% BSA and 100 mM KCl). Phosphorylation reactions were initiated by adding 19 µl of 2X Enzyme solution (6.4 nM active Akt/PKB, 1X Assay Buffer, 5% glycerol, 1 mM DTT, 1X PIC and 0.1% BSA). The reactions were then incubated at room temperature for 45 minutes.

Step 2:

The reaction was stopped by adding 170 µl of 125 mM EDTA. 200 µl of stopped reaction was transferred to a Streptavidin Flashplate® PLUS (NEN Life Sciences, catalog no. SMP103). The plate was incubated for ≥10 minutes at room temperature on a plate shaker. The contents of each well was aspirated, and the wells rinsed 2 times with 200 µl TBS per well. The wells were then washed 3 times for 5 minutes with 200 µl TBS per well with the plates incubated at room temperature on a platform shaker during wash steps.

The plates were covered with sealing tape and counted using the Packard TopCount with the appropriate settings for counting [$^{33}$P] in Flashplates.

Procedure for Streptavidin Filter Plate Assay:

Step 1:

The enzymatic reactions as described in Step 1 of the Streptavidin Flash Plate Assay above were performed.

Step 2:

The reaction was stopped by adding 20 µl of 7.5M Guanidine Hydrochloride. 50 µl of the stopped reaction was transferred to the Streptavidin filter plate (SAM$^{2™}$ Biotin Capture Plate, Promega, catalog no. V7542) and the reaction was incubated on the filter for 1-2 minutes before applying vacuum.

The plate was then washed using a vacuum manifold as follows: 1) 4 x 200 µl/well of 2M NaCl; 2) 6 x 200 µl/well of 2M NaCl with 1% $H_3PO_4$; 3) 2 x 200 µl/well of di$H_20$; and 4) 2 x 100 µl/well of 95% Ethanol. The membranes were then allowed to air dry completely before adding scintillant.

The bottom of the plate was sealed with white backing tape, 30 µl/well of Microscint 20 (Packard Instruments, catalog no. 6013621) was added. The top of the plate was sealed with clear sealing tape, and the plate then counted using the Packard TopCount with the appropriate settings for [$^{33}$P] with liquid scintillant.

Procedure for Phosphocellulose Filter Plate Assay:

Step 1:

The enzymatic reactions were performed as described in Step 1 of the Streptavidin Flash Plate Assay (above) utilizing KKGGRARTSSFAEPG (SEQ.ID.NO.: 16) as the substrate in place of biotin-GGRARTSSFAEPG.

Step 2:

The reaction was stopped by adding 20 µl of 0.75% $H_3PO_4$. 50 µl of stopped reaction was transferred to the filter plate (UNIFILTER™, Whatman P81 Strong Cation Exchanger, White Polystyrene 96 Well Plates, Polyfiltronics, catalog no. 7700-3312) and the reaction incubated on the filter for 1-2 minutes before applying vacuum.

The plate was then washed using a vacuum manifold as follows: 1) 9 x 200 µl/well of 0.75% $H_3PO_4$; and 2) 2 x 200 µl/well of di$H_20$. The bottom of the plate was sealed with white backing tape, then 30 µl/well of Microscint 20 was added. The top of the plate was sealed with clear sealing tape, and the plate counted using the Packard TopCount with the appropriate settings for [$^{33}$P] and liquid scintillant.

PKA assay:

Each individual PKA assay consists of the following components:

A. 5X PKA assay buffer (200 mM Tris pH7.5, 100 mM $MgCl_2$, 5mM ϑ-mercaptoethanol, 0.5 mM EDTA)

B. 50 µM stock of Kemptide (Sigma) diluted in water

C. $^{33}$P-ATP prepared by diluting 1.0 µl $^{33}$P-ATP [10 mCi/ml] into 200 Tl of a 50 µM stock of unlabeled ATP

D. 10 µl of a 70 nM stock of PKA catalytic subunit (UBI catalog # 14-114) diluted in 0.5 mg/ml BSA

E. PKA/Kemptide working solution: equal volumes of 5X PKA assay buffer, Kemptide solution and PKA catalytic subunit.

The reaction is assembled in a 96 deep-well assay plate. The inhibitor or vehicle (10 Tl) is added to 10 Tl of the $^{33}$P-ATP solution. The reaction is initiated by adding 30 Tl of the PKA/Kemptide working solution to each well. The reactions were mixed and incubated at room temperature for 20 min. The reactions were stopped by adding 50 Tl of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing.

The enzyme reaction product (phosphorylated Kemptide) was collected on p81 phosphocellulose 96 well filter plates (Millipore). To prepare the plate, each well of a p81 filter plate was filled with 75 mM phosphoric acid. The wells were emptied through the filter by applying a vacuum to the bottom of the plate. Phosphoric acid (75 mM, 170 µl) was added to each well. A 30 µl aliquot from each stopped PKA reaction was added to corresponding wells on the filter plate containing the phosphoric acid. The peptide was trapped on the filter following the application of a vacuum and the filters were washed 5 times with 75 mM phosphoric acid. After the final wash, the filters were allowed to air dry. Scintillation fluid (30 µl) was added to each well and the filters counted on a TopCount (Packard).

PKC assay:

Each PKC assay consists of the following components:

A. 10X PKC co-activation buffer: 2.5 mM EGTA, 4mM $CaCl_2$

B. 5X PKC activation buffer: 1.6 mg/ml phosphatidylserine, 0.16 mg/ml diacylglycerol, 100 mM Tris pH 7.5, 50 mM $MgCl_2$, 5 mM θ-mercaptoethanol

C. $^{33}$P-ATP prepared by diluting 1.0 µl $^{33}$P-ATP [10 mCi/ml] into 100µl of a 100 µM stock of unlabeled ATP

D. Myelin basic protein (350 µg/ml, UBI) diluted in water

E. PKC (50ng/ml, UBI catalog # 14-115) diluted into 0.5 mg/ml BSA

F. PKC/Myelin Basic Protein working solution: Prepared by mixing 5 volumes each of PKC co-activation buffer and Myelin Basic protein with 10 volumes each of PKC activation buffer and PKC.

The assays were assembled in 96 deep-well assay plates. Inhibitor or vehicle (10 Tl) was added to 5.0 ul of $^{33}$P-ATP. Reactions were initiated with the addition of the PKC/Myelin Basic Protein working solution and mixing. Reactions were incubated at 30°C for 20 min. The reactions were stopped by adding 50 Tl of 100 mM EDTA and 100 mM sodium pyrophosphate and mixing. Phosphorylated Mylein Basic Protein was collected on PVDF membranes in 96 well filter plates and quantitated by scintillation counting.

Compounds of the instant invention described in the Schemes and Tables were tested in the assay described above and were found to have $IC_{50}$ of $\leq$ 50 µM against one or more of Akt1, Akt2 and Akt3.

EXAMPLE 5

Cell based Assays to Determine Inhibition of Akt/PKB

Cells (for example LnCaP or a PTEN$^{(-/-)}$tumor cell line with activated Akt/PKB) were plated in 100 mM dishes. When the cells were approximately 70 to 80% confluent, the cells were refed with 5 mls of fresh media and the test compound added in solution. Controls included untreated cells, vehicle treated cells and cells treated with either LY294002 (Sigma) or wortmanin (Sigma) at 20 μM or 200 nM, respectively. The cells were incubated for 2, 4 or 6 hrs, and the media removed, the cells were washed with PBS, scraped and transferred to a centrifuge tube. They were pelleted and washed again with PBS. Finally, the cell pellet was resuspended in lysis buffer (20 mM Tris pH8, 140 mM NaCl, 2 mM EDTA, 1% Triton, 1 mM Na Pyrophosphate, 10 mM θ-Glycerol Phosphate, 10 mM NaF, 0.5 mm $NaVO_4$, 1 μM Microsystine, and 1x Protease Inhibitor Cocktail), placed on ice for 15 minutes and gently vortexed to lyse the cells. The lysate was spun in a Beckman tabletop ultra centrifuge at 100,000 x g at 4°C for 20min. The supernatant protein was quantitated by a standard Bradford protocol (BioRad) and stored at –70°C until needed.

Proteins were immunoprecipitated (IP) from cleared lysates as follows: For Akt1/PKBI, lysates are mixed with Santa Cruz sc-7126 (D-17) in NETN (100mM NaCl, 20mM Tris pH 8.0, 1mM EDTA, 0.5% NP-40) and Protein A/G Agarose (Santa Cruz sc-2003) was added. For Akt2/PKBθ, lysates were mixed in NETN with anti-Akt2 agarose (Upstate Biotechnology #16-174) and for Akt3/PKBK, lysates were mixed in NETN with anti-Akt3 agarose (Upstate Biotechnology #16-175). The IPs were incubated overnight at 4°C, washed and seperated by SDS-PAGE.

Western blots were used to analyze total Akt, pThr308 Akt1, pSer473 Akt1, and corresponding phosphorylation sites on Akt2 and Akt3, and downstream targets of Akt using specific antibodies (Cell Signaling Technology): Anti-Total Akt (cat. no. 9272), Anti-Phopho Akt Serine 473 (cat. no. 9271), and Anti-Phospho Akt Threonine 308 (cat. no. 9275). After incubating with the appropriate primary antibody diluted in PBS + 0.5% non-fat dry milk (NFDM) at 4 °C overnight, blots were washed, incubated with Horseradish peroxidase (HRP)-tagged secondary antibody in PBS + 0.5% NFDM for 1 hour at room temperature. Proteins were detected with ECL Reagents (Amersham/Pharmacia Biotech RPN2134).

EXAMPLE 6

Heregulin Stimulated Akt Activation

MCF7 cells (a human breast cancer line that is PTEN$^{+/+}$) were plated at 1x10$^6$ cells per 100mM plate. When the cells were 70 – 80% confluent, they were refed with 5 ml of serum free media and incubated overnight. The following morning, compound was added and the cells were incubated for 1 – 2 hrs, after which time heregulin was added (to induce the activation of Akt) for 30 minutes and the cells were analyzed as described above.

EXAMPLE 7

Inhibition Of Tumor Growth

In vivo efficacy of an inhibitor of the growth of cancer cells may be confirmed by several protocols well known in the art.

Human tumor cell lines which exhibit a deregulation of the PI3K pathway (such as LnCaP, PC3, C33a, OVCAR-3, MDA-MB-468, A2780 or the like) are injected subcutaneously into the left flank of 6-10 week old female nude (also male mice [age 10-14 weeks] are used for prostate tumor xenografts [LnCaP and PC3]) mice (Harlan) on day 0. The mice are randomly assigned to a vehicle, compound or combination treatment group. Daily subcutaneous administration begins on day 1 and continues for the duration of the experiment. Alternatively, the inhibitor test compound may be administered by a continuous infusion pump. Compound, compound combination or vehicle is delivered in a total volume of 0.2 ml. Tumors are excised and weighed when all of the vehicle-treated animals exhibited lesions of 0.5 - 1.0 cm in diameter, typically 4 to 5.5 weeks after the cells were injected. The average weight of the tumors in each treatment group for each cell line is calculated.

EXAMPLE 8

Spot Multiplex Assay

This procedure describes a sandwich immunoassay used to detect multiple phosphorylated proteins in the same well of a 96 well format plate. Cell lysates are incubated in 96-well plates on which different capture antibodies are placed on spatially distinct spots in the same well. Phoshorylation-specific rabbit polyclonal antibodies are added and the complex is detected by an anti-rabbit antibody labeled with an electrochemiluminescent tag.

96-Well LNCaP plates +/- Compounds:

Spin in Beckman J6 1200 rpm 10 min, aspirate media. Add 50µl/well: TBS (Pierce #28376-20mM Tris pH 7.5, 150mM NaCl) + 1% Triton X-100 + Protease and Phosphatase Inhibitors. Wrap in plastic wrap, place in -70°C freezer until completely frozen. Block Multiplex Plates (Meso Scale Discovery, Gaithersburg, MD) with 3% Blocker A in 1X Tris Wash Buffer, 150µl/well. Cover with plate sealer, incubate on Micromix shaker RT 2h (minimum). Wash with 1X RCM 51 (TTBS). Thaw cell lysate plates on ice, add 40µl lysate/well into blocked plates. Cover with plate sealer, incubate on Micromix shaker 4°C O/N, Wash with 1X RCM 51. Dilute Secondary Antibodies in 1% Blocker A in 1X Tris Wash Buffer: Anti phospho AKT (T308), Anti phospho Tuberin (T1462), alone or in combination. Add 25µl/well, cover with plate sealer, incubate on Micromix shaker RT 3h. Wash with 1X RCM 51. Dilute Ru-GAR in 1% Blocker A in 1X Tris Wash Buffer. Add 25µl/well, cover with plate sealer, incubate on Micromix shaker RT 1h. Wash with 1X RCM 51. Dilute 4X Read Buffer T to 1X with Water, add 200µl diluted Read Buffer/well

Read on Sector 6000 Imager.

Protease and Phosphatase Inhibitors:

Microcystin-LR, Calbiochem # 475815 to 1 µM final concentration (stock=500µM)

Calbiochem # 524624, 100X Set I

Calbiochem # 524625, 100X Set II

120

Calbiochem # 539134, 100X Set III

Anti Phospho AKT (T308):

Cell Signaling Technologies # 9275

Anti Phospho Tuberin (T1462):

Covance Affinity Purified (Rabbits MS 2731/2732)

Ru-GAR = Ruthenylated Goat anti Rabbit

10X Tris Wash Buffer, Blocker A and 4X Read Buffer T

10X RCM 51 (10X TTBS, RCM 51)

1X = 20mM Tris pH 7.5, 140mM NaCl, 0.1% Tween-20

EXAMPLE 9

Cell-Based (In-vivo) Assay

This procedure describes a cell-based (in vivo) activity assay for the Akt serine/threonine kinase. Activated endogenous Akt is capable of phosphorylatinga specific Akt substrate (GSK3β) peptide which is biotinylated. Detection is performed by Homogeneous Time Resolved Fluorescence (HTRF) using a Europium Kryptate [Eu(K)] coupled antibody specific for the phosphopeptide and streptavidin linked XL665 fluorophore which will bind to the biotin moiety on the peptide. When the [Eu(K)] and XL665 are in proximity (i.e. bound to the same phosphopeptide molecule) a non-radiative energy transfer takes place from the Eu(K) to the XL665, followed by emission of light from XL665 at 665 nm.

The assay can be used to detect inhibitors of all three Akt isozymes (Akt1, Akt2, and Akt3) from multiple different species if specific antibodies to each exist.

MATERIALS AND REAGENTS

A. Cell Culture Microtiter Flat Bottom 96 well plates, Corning Costar, Catalog no. 3598

B. Reacti-Bind Protein A Coated 96-well plates, Pierce, Catalog no 15130.

C. Reacti-Bind Protein G Coated 96-well plates, Pierce, Catalog no 15131.

D. Micromix 5 Shaker.

E. Microfluor®B U Bottom Microtiter Plates, Dynex Technologies, Catalog no. 7205.

F. 96 Well Plate Washer, Bio-Tek Instruments, Catalog no. EL 404.

G. Discovery® HTRF Microplate Analyzer, Packard Instrument Company.

BUFFER SOLUTIONS

A. IP Kinase Cell Lysis Buffer: 1X TBS; 0.2% Tween 20; 1X Protease Inhibitor Cocktail III (Stock is 100X, Calbiochem, 539134); 1X Phosphatase Inhibitor Cocktail I (Stock is 100X, Calbiochem, 524624); and 1X Phosphatase Inhibitor Cocktail II (Stock is 100X, Calbiochem, 524625).

B. 10X Assay Buffer: 500 mM Hepes pH 7.5; 1% PEG; 1 mM EDTA; 1 mM EGTA; and 20 mM β-glycerophosphate.

C. IP Kinase Assay Buffer: 1X Assay Buffer; 50 mM KCl; 150 μM ATP; 10 mM $MgCl_2$; 5% Glycerol; 1 mM DTT; 1 Tablet Protease Inhibitor Cocktail per 50 ml Assay Buffer; and 0.1% BSA

D. GSK3β Substrate Solution: IP Kinase Assay Buffer; and 500 nM Biotinylated GSK3β peptide.

E. Lance Buffer: 50 mM Hepes pH 7.5; 0.1% BSA; and 0.1%Triton X-100.

F. Lance Stop Buffer: Lance Buffer; and 33.3 mM EDTA.

G. Lance Detection Buffer: Lance Buffer; 13.3 μg/ml SA-APC; and 0.665 nM EuK Ab a-phospho (Ser-21) GSK3ß

Multi-Step Immunoprecipitation Akt Kinase Assay

Day1

A. Seed C33a cells Step: Plate 60,000 C33a cells/well in 96 well microtiter plate.

B. Incubate cells overnight at 37°C.

Day 2

D. Compound Addition Step: Add compounds in fresh media (alpha-MEM/10% FBS, room temp) to 96 well plate from above and incubate for 5 hrs in tissue culture incubator.

E. Cell Lysis Step: Aspirate media and add 100 μl of IP Kinase Cell Lysis Buffer.

F. Freeze 96 well microtiter plate at -70°C (NOTE: This step can be done for a minimum of 1 hour or overnight.)

Day 3

G. Coat Protein A/G 96 well plate Step: Add appropriate concentration of α-Akt antibody (Akt1, Akt2, or Akt3) in a 100 μl of PBS to the following wells:

| | |
|---|---|
| α-Akt 1 (20 ng/well/100ul) | B2 >>>>>> B10 / rows B – G / Akt1 plate |
| α-Akt 2 (50 ng/well/100ul) | B2 >>>>>> B10 / rows B – G / Akt2 plate |
| Rabbit-IgG (150 ng/well/100 ul): | B11 – G11 on every plate (Akt1 and Akt2) |

H. Incubate in the cold room (+4°C) for 4 hours on the Micromix 5 (Form 20; Attitude 2) (NOTE: Attitude depends on which Micromix 5 machine).

I. Aspirate off α-Akt antibody solution and add 100 μl of PBS to each well.

J. Akt Immunoprecipitation Step: To the 100 μl of PBS from Step(I) add 5 μl of thawed cell lystate for Akt1 plates and 10 μl of thawed cell lysate for Akt2 plates. NOTE: Thaw cell lysate on ice. Mix thawed lysate by pipetting up & down 10X before transferring to antibody plates. Keep the cell lysate plates on ice. After transfer of cell lysate to the antibody plates refreeze the cell lysate plates at -70°C.

K. Incubate in the cold room (+4°C) overnight on Micromix 5 shaker (form 20, attitude 3).

Day 4

L. Immunoprecipitation Plate Wash Step: Wash 96 well plates 1X with TTBS (RCM 51, 1X = 2 cycles) using the 96-Well Plate Washer. Fill wells with TTBS and incubate for 10 minutes. Wash 96 well plates 2X with TTBS. (NOTE: Prime plate washer before use: 1. Check buffer reservoirs, making sure they are full and 2. empty waste containers.

M. Manual Plate Wash Step: Add 180 μl of IP Kinase Assay buffer.

N. Start Akt Enzyme Reaction: Aspirate supernatant. Add 60 μl of GSK3β Substrate Solution.

O. Incubate for 2.5 hours on Micromix 5 shaker @ RT. NOTE: Time of incubation should be adjusted so that the ratio of Column 10 /Column 11 is not >10.

P. Combine 30 µl of Lance Detection Buffer with 30 µl of Lance Stop Buffer (60 µl total/well) and add to Microfluor U bottom 96 well black plates.

Q. Stop Akt Enzyme Reaction: Transfer 40 µl of Akt Enzyme Reaction Mix from Protein A/G 96 well plate from Step (O) to Microfluor U bottom 96 well black plates from Step (P).

U. Incubate at room temperature for 1-2 hrs on Micromix 5 shaker (form 20, attitude 3), then read with the Discovery HTRF Microplate Analyzer using Akt program.

IP Kinase Cell Lysis Buffer

100 µl per well

| | 8 ml (1 Plate) | | 45 ml (6 Plates) |
|---|---|---|---|
| 1X TBS | 7744 µl | | NA |
| Tween 20 | 20 µl | | NA |
| 1X Protease Inhibitor Cocktail III | 80 µl | | NA |
| 1X Phosphatase Inhibitor Cocktail I | | | 450 µl |
| 1X Phosphatase Inhibitor Cocktail II | 80 µl | | 450 µl |
| Microcystin LR (500X) | | | 450 µl |
| | 80 µl | | |
| | | | 90 µl |

IP Kinase Assay Buffer

100 µl per well

| | 8 ml (1 Plate) | | 50 ml (3 Plates) |
|---|---|---|---|
| 10X Assay Buffer | 800 µl | | 5 ml |
| 1 M KCl | 400 µl | | 2.5 ml |
| 250 mM ATP | 4.8 µl | | 30 µl |
| 1M $MgCl_2$ | 80 µl | | 500 µl |
| Glycerol | 400 µl | | 2.5 ml |
| 1M DTT | 8 µl | | 50 µl |
| Protease Inhibitor Cocktail | 1 tablet/50 ml | | 1 |
| 10% BSA | 80 µl | | 500 µl |
| di $dH_20$ | 6227.2 µl | | 38.9 ml |

GSK3ß Substrate Solution

60 µl per well

| | 5 ml (1 Plate) | | 7 ml |
|---|---|---|---|

| | | | |
|---|---|---|---|
| IP Kinase Assay Buffer<br>1 mM GSK3ß peptide | 5 ml<br>2.5 µl | | -<br>3.5 µl |

Lance Stop Buffer

30 µl per well

| | | | |
|---|---|---|---|
| | 3 ml<br>(1 Plate) | 5 ml | 5 ml |
| 1X Lance Buffer<br>EDTA 0.5 M | 2800.2 µl<br>199.8 µl | | |

Lance Detection Buffer

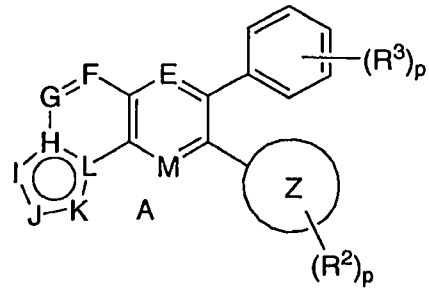
30 µl per well

| | | | |
|---|---|---|---|
| | 3 ml<br>(1 Plate) | | 5 ml |
| SA-APC (1 mg/ml in ddH2O, dilute 1/75.2 in Lance Buffer)<br>EuK Ab a-phospho (Ser 21)GSK3ß (680 nM, dilute 1/1133 in Lance Buffer) | 40 µl<br>2.7 µl | | 66.7 µl<br>4.5 µl |

5

WHAT IS CLAIMED IS:

1. A compound according to Formula A:




wherein:

E, F, G, H, I, J, K, L and M are independently selected from: C or N, wherein each E, F, G, H, I, J, K, L and M is optionally substituted with $R^1$;

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2; p is independently 0, 1, 2, 3, 4 or 5;

Ring Z is selected from: $(C_3\text{-}C_8)$cycloalkyl, aryl, heteroaryl and heterocyclyl;

$R^1$ is selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^2$ is independently selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, SH, $S(O)_mNR^7R^8$, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^3$ is independently selected from: oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b$ $(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^6$ is: $(C=O)_aO_bC_1$-$C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2$-$C_{10}$ alkenyl, $C_2$-$C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1$-$C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1$-$C_{10})$alkyl or $(C=O)_aO_bC_3$-$C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1$-$C_{10})$alkyl, $O_a(C_1$-$C_3)$perfluoroalkyl, $(C_0$-$C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, $(C_3$-$C_6)$cycloalkyl, $(C_0$-$C_6)$alkylene-aryl, $(C_0$-$C_6)$alkylene-heterocyclyl, $(C_0$-$C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0$-$C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0$-$C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1$-$C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1$-$C_6)$alkyl, oxo, and $N(R^b)_2$;

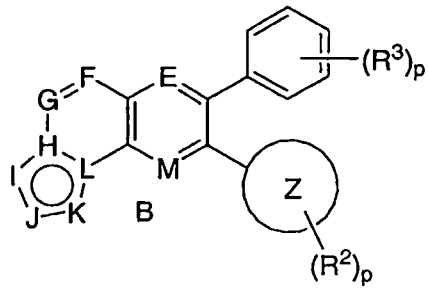
$R^7$ and $R^8$ are independently selected from: H, $(C=O)_aO_b(C_1$-$C_{10})$alkyl, $(C=O)_aO_b(C_3$-$C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from $R^{6a}$;

$R^a$ is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, aryl, or heterocyclyl; and

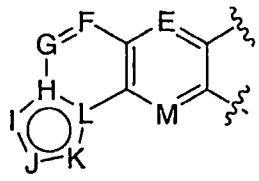
$R^b$ is independently: H, $(C_1$-$C_6)$alkyl, aryl, heterocyclyl, $(C_3$-$C_6)$cycloalkyl, $(C=O)_aO_b(C_1$-$C_6)$alkyl, or $S(O)_mR^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

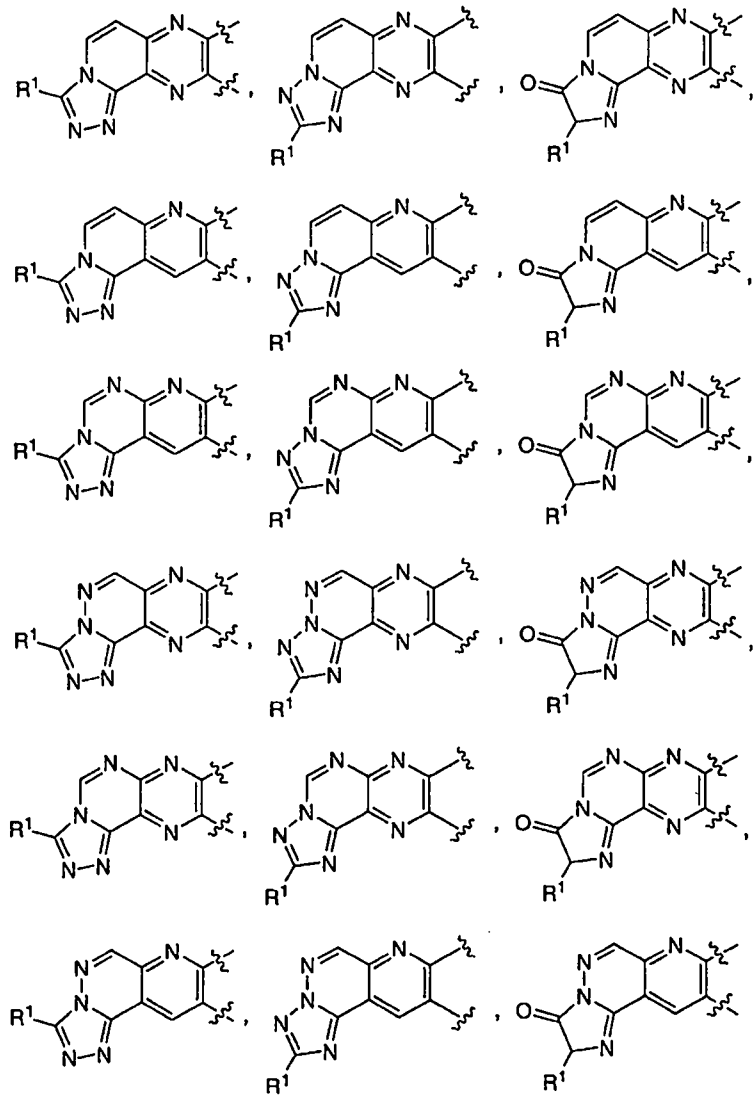
2. A compound according to Formula B:



wherein:



is selected from:



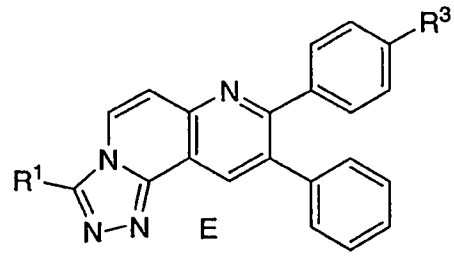
;

$R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

and all other substituents and variables are as defined in Claim 1;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

3. A compound according to Formula E:



wherein:

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;

$R^1$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^3$ is selected from: H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one or more substituents selected from $R^6$;

$R^6$ is: $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one or more substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl,

$(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$;

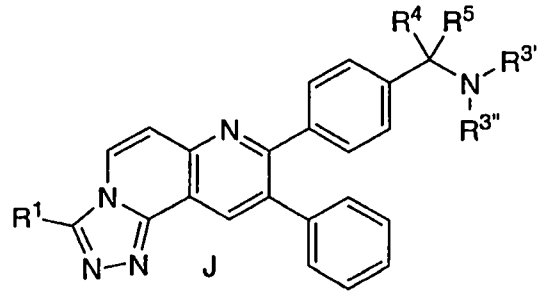
$R^7$ and $R^8$ are independently selected from: H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one or more substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one or more substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

$R^b$ is independently: H, $(C_1\text{-}C_6)$alkyl, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C=O)_aO_b(C_1\text{-}C_6)$alkyl, or $S(O)_mR^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

4. A compound according to Formula J:




J

wherein:

a is 0 or 1; b is 0 or 1; m is 0, 1 or 2;

$R^1$ is selected from: $CF^3$, H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m$-$(C_1\text{-}C_{10})$alkyl and $(C=O)_aO_b$-heterocyclyl,

said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one to six substituents selected from $R^6$;

$R^{3'}$ and $R^{3''}$ are independently selected from: $CF^3$, H, oxo, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkenyl, $(C=O)_aO_b(C_2\text{-}C_{10})$alkynyl, $CO_2H$, halo, OH, $O_b(C_1\text{-}C_6)$perfluoroalkyl, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_6)$alkyl-heterocyclyl and $(C=O)_aO_b$-heterocyclyl, said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl is optionally substituted with one to five substituents selected from $R^6$; or $R^{3'}$ and $R^{3''}$ can be taken together with the nitrogen to which they are attached to form a piperidine or pyrrolidine which may be optionally substituted with one to five substituents selected from $R^6$;

$R^4$ and $R^5$ are independently: H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, $(C_1\text{-}C_6)$alkynyl, wherein said alkyl is optionally substituted with up to three substituents selected from: OH and halo; and wherein $R^4$ and $R^5$ can be taken together to form a $(C_3\text{-}C_7)$cycloalkyl, wherein said cycloalkyl is optionally substituted with up to three substituents selected from $R^6$;

$R^6$ is: $CF^3$, $(C=O)_aO_bC_1\text{-}C_{10}$ alkyl, $(C=O)_aO_b$aryl, $C_2\text{-}C_{10}$ alkenyl, $C_2\text{-}C_{10}$ alkynyl, $(C=O)_aO_b$ heterocyclyl, $CO_2H$, halo, CN, OH, $O_bC_1\text{-}C_6$ perfluoroalkyl, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m\text{-}(C_1\text{-}C_{10})$alkyl or $(C=O)_aO_bC_3\text{-}C_8$ cycloalkyl, said alkyl, aryl, alkenyl, alkynyl, heterocyclyl, and cycloalkyl optionally substituted with one to five substituents selected from $R^{6a}$;

$R^{6a}$ is selected from: $CF^3$, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $O_a(C_1\text{-}C_3)$perfluoroalkyl, $(C_0\text{-}C_6)$alkylene-$S(O)_mR^a$, SH, oxo, OH, halo, CN, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_0\text{-}C_6)$alkylene-aryl, $(C_0\text{-}C_6)$alkylene-heterocyclyl, $(C_0\text{-}C_6)$alkylene-$N(R^b)_2$, $(C=O)_aNR^b{}_2$, $C(O)R^a$, $(C_0\text{-}C_6)$alkylene-$CO_2R^a$, C(O)H, and $(C_0\text{-}C_6)$alkylene-$CO_2H$, said alkyl, alkenyl, alkynyl, cycloalkyl, aryl, and heterocyclyl is optionally substituted with up to three substituents selected from $R^b$, OH, $(C_1\text{-}C_6)$alkoxy, halogen, $CO_2H$, CN, $O_a(C=O)_b(C_1\text{-}C_6)$alkyl, oxo, and $N(R^b)_2$;

$R^7$ and $R^8$ are independently selected from: $CF^3$, H, $(C=O)_aO_b(C_1\text{-}C_{10})$alkyl, $(C=O)_aO_b(C_3\text{-}C_8)$cycloalkyl, $(C=O)_aO_b$-aryl, $(C=O)_aO_b$-heterocyclyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, SH, $SO_2R^a$, and $(C=O)_aNR^b{}_2$, said alkyl, cycloalkyl, aryl, heterocylyl, alkenyl, and alkynyl is optionally substituted with one to five substituents selected from $R^{6a}$, or $R^7$ and $R^8$ can be taken together with the nitrogen to which they are attached to form a monocyclic or bicyclic heterocycle with 3-7 members in each ring and optionally containing, in addition to the nitrogen, one or two additional heteroatoms selected from N, O and S, said monocylcic or bicyclic heterocycle optionally substituted with one to six substituents selected from $R^{6a}$;

$R^a$ is $(C_1\text{-}C_6)$alkyl, $NR^b{}_2$, $(C_3\text{-}C_6)$cycloalkyl, aryl, or heterocyclyl; and

$R^b$ is independently: H, $(C_1\text{-}C_6)$alkyl, $NH_2$, aryl, heterocyclyl, $(C_3\text{-}C_6)$cycloalkyl, $(C{=}O)_aO_b(C_1\text{-}C_6)$alkyl, or $S(O)_mR^a$;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

5. A compound which is selected from:

9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-amine;
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-ol;
9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine;
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-thiol;
3-methyl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4 ]triazolo[3,4-f]-1,6-naphthyridine;
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-(chloromethyl)-9-phenyl-8-(4-{[4-(4-pyridin-2-yl-1H-imidazol-1-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-[(4-methylpiperazin-1-yl)methyl]-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
2-({[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-1H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}amino)ethanol;
8-(4-Aminomethyl-phenyl)-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-3-ol;
1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
4-(3-Methyl-9-phenyl-[1,2,4]triazolo[3,4-*f*][1,6]naphthyridin-8-yl)-benzylamine;
8-[4-(Aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-amine;
1-[4-(9-Phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine;
9-Phenyl-8-{4-[4-(5-pyridin-2-yl-4*H*-[1,2,4]triazol-3-yl)-piperidin-1-ylmethyl]-phenyl}-[1,2,4] triazolo[3,4-*f*][1,6]naphthyridine;
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;

3-(1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
tert-butyl [9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl) [1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-yl]methylcarbamate;
[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol;
5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]-2,4-dihydro-3H-1,2,4-triazol-3-one;
3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-imidazo[2,1-b][1,3] thiazol-6-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-[1,2,4]triazolo [1,5-a]pyrimidin-2-yl[1,2,4] triazolo[3,4-f]-1,6-naphthyridine;
3-imidazo[1,2-a]pyridin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,4-triazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-(1H-benzimidazol-6-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3;4-f]-1,6-naphthyridine;
5-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine;
9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]pyridin-2-amine;
4-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol;
3-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol;

2-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]phenol;

1-{4-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide;

1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]piperidine-4-carboxamide;

9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;

9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)-3-(1H-1,2,3-triazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrimidin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;

3-(1-methyl-1H-imidazol-4-yl)-9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridine;

N-[2-(4-methyl-1H-imidazol-2-yl)ethyl]-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amine;

$N^1$-(2-hydroxyphenyl)-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-beta-alaninamide;

1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide;

5-[({4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}amino)methyl]pyridin-2-ol;

$N^1$,$N^1$,2,2-tetramethyl-$N^3$-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propane-1,3-diamine;

3-hydroxy-2,2-dimethyl-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine;

2-fluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine;

2,2-difluoro-3-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine;

2,3-dihydroxy-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine;

4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine;

4-hydroxy-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl] cyclohexanamine;

3-hydroxy-2,2-dimethyl-N-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}propan-1-amine;

3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine;

3-hydroxy-2,2-dimethyl-N-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]propan-1-amine;

3-hydroxy-2,2-dimethyl-N-{4-[9-phenyl-3-(1H-1,2,3-triazol-4-yl) [1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] benzyl}propan-1-amine;

tert-butyl {[8-(4-{[(3-hydroxy-2,2-dimethylpropyl)amino]methyl}phenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methyl}carbamate;

N-{4-[3-(ammoniomethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-3-hydroxy-2,2-dimethylpropan-1-amine;

[9-phenyl-8-(4-{[4-(5-pyrazin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1yl]methyl}phenyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol;

$N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(2-hydroxyphenyl)-beta-alaninamide;

(8-{4-[(cyclohexylamino)methyl]phenyl}-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl)methanol;

$N^3$-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzyl}-$N^1$-(4-hydroxyphenyl)-beta-alaninamide;

[9-phenyl-8-(4-{[4-(5-pyridin-3-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl)[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl]methanol;

1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzyl}piperidine-4-carboxamide;

{8-[4-(1-aminocyclopropyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol;

1-[4-(9-phenyl-3-pyridin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;

1-{4-[3-(1-oxidopyridin-3-yl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl] phenyl}methanamine;

1-[4-(3,9-diphenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;

1-{4-[3-(4-fluorophenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;

4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}benzonitrile;

4-(9-phenyl-3-pyrimidin-4-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine;

1-{4-[3-(1-oxidopyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;

5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}yridine-2-ol;

1-[4-(9-phenyl-3-pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;

4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzylamine;

1-[4-(9-phenyl-3-pyridin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-[4-(9-phenyl-3-pyrazin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-{4-[9-phenyl-3-(1H-1,2,4-triazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(3-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(3-methyl-1H-1,2,4-triazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(1-methyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1,2,5-thiadiazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1,2,3-thiadiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanamine;
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methanol;
1-{4-[9-phenyl-3-(2,2,2-trifluoroethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1H-tetraazol-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridine-3-carboxamide;
1-{4-[3-(1H-imidazol-1-ylmethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-(4-{3-[(methylsulfonyl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine;
{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}acetonitrile;
2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol;
N-({8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}methyl)acetamide;
4-[3-(2-methylimidazo[1,2-a]pyridin-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyridin-3-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-[4-(3-imidazo[1,2-a]pyridin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1,2-benzisoxazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;

1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-{4-[3-(1-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
4-[3-(1-methyl-5-phenyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1-benzothien-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(1-isopropyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-(4-{9-phenyl-3-[(2S)-pyrrolidin-2-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine;
4-[3-(1-aminoethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[3-(1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-[4-(3-cyclopropyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-{4-[9-phenyl-3-(trifluoromethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(5-methyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
4-[3-(1H-indol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylaminen;
1-{4-[3-(1-methyl-1H-imidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(3-methyl-2H-3lambda$^5$-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
4-[3-(6-chloroimidazo[1,2-a]pyridin-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[3-(1H-benzimidazol-2-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
4-[3-(5-cyclopropyl-4H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-1H-indazol-3-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
4-[9-phenyl-3-(3-phenyl-1H-pyrazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;

1-(4-{9-phenyl-3-[3-(trifluoromethyl)-1H-pyrazol-5-yl][1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine;
1-[4-(9-phenyl-3-pyrazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-{4-[3-(1-benzyl-1H-pyrazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
4-[9-phenyl-3-(1-phenyl-1H-pyrazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[9-phenyl-3-(4,5,6,7-tetrahydro-2-benzothien-1-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-2-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}propan-2-amine;
1-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethane-1,2-diol;
4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}imidazolidin-2-one;
(2R)-2-amino-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}ethanol;
(2R)-2-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2-(methylamino)ethanol;
1-{4-[3-(5-ethylisoxazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
5-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-2,4-dihydro-3H-1,2,4-triazol-3-one;
6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-4,5-dihydropyridazin-3(2H)-one;
6-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}pyridazin-3(2H)-one;
N-(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)acetamide;
1-{4-[3-(4-phenoxyphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(1H-benzimidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
(4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}phenyl)methanol;
4-[3-(4-cyclohexylphenyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
4-{8-[4-(aminomethyl)phenyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-3-yl}-1,3-dihydro-2H-imidazol-2-one;
1-{4-[3-(4-methyl-1H-imidazol-5-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;

4-[9-phenyl-3-(1-propyl-1H-imidazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[3-(1-isopropyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[3-(1-butyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-[4-(3-imidazo[1,2-a]pyrimidin-2-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
5-({[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amino}methyl)pyridin-2-ol;
1-(6-methoxypyridin-3-yl)-N-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]methanamine;
N-[(2-methoxypyrimidin-5-yl)methyl]-N-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amine;
1-[4-(3-ethyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
1-[4-(9-phenyl-3-propyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]methanamine;
N-[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]acetamide;
4-({[4-(9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)benzyl]amino}methyl)phenol;
1-[9-phenyl-8-(4-{[4-(5-pyridin-2-yl-4H-1,2,4-triazol-3-yl)piperidin-1-yl] methyl}phenyl)[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-3-yl]methanamine;
9-phenyl-3-(1H-1,2,3-triazol-4-yl)-8-(4-{[4-(4H-1,2,4-triazol-3-yl)piperidin-1-yl]methyl}phenyl) [1,2,4]triazolo[3,4-f]-1,6-naphthyridine;
1-{4-[3-(1H-Imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(3H-1lambda$^4$,3-thiazol-5-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1H-pyrazol-3-yl)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
1-{4-[9-phenyl-3-(1,3-thiazol-4-yl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}methanamine;
4-[9-Phenyl-3-(pyrrolidin-1-ylmethyl)[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
1-{4-[3-(azetidin-1-ylmethyl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine;
1-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)piperidine-4-carboxamide;
1-{4-[3-(morpholin-4-ylmethyl)-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl} methanamine;
2-[({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)amino]ethanol;
1-(4-{3-[(4-methyl piperazin-1-yl)methyl]-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl}phenyl)methanamine;

4-[9-phenyl-3-(piperazin-1-ylmethyl)[1,2,4]triazolo [3,4-f]-1,6-naphthyridin-8-yl]benzylamine;
N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N-methylamine;
N-({8-[4-(aminomethyl) phenyl]-9-phenyl[1,2,4] triazolo[3,4-f]-1,6-naphthyridin-3-yl} methyl)-N,N-dimethylamine;
[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]methanol;
{4-[3-(1-Methyl-1*H*-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}methanol;
1-[4-(9-Phenyl-3-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanol;
9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;
3-methyl-9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl)piperidin-1-yl] methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;
9-phenyl-8-(4-{[4-(4*H*-1,2,4-triazol-3-yl) piperidin-1-yl]methyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-3-ol;
1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropanamine;
1-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl] phenyl}cyclo propanamine;
1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-*a*] pyrimidin-2-yl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl] cyclopropanamine;
1-{4-[9-phenyl-3-(5,6,7,8-tetrahydro imidazo[1,2-a]pyridin-2-yl)[1,2,4] triazolo [3,4-f]-1,6-naphthyridin -8-yl] phenyl}cyclo propanamine;
1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]cyclopropanamine;
1-{4-[3-(1,5-dimethyl-1H-pyrazol-3-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}cyclopropanamine;
(1R)-1-[4-(3-Methyl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl ]ethanamine;
(1*R*)-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethanamine;
(1*R*)-1-{4-[9-Phenyl-3-(5-pyridin-2-yl-1*H*-pyrazol-3-yl)[1,2,4]triazolo[3,4-*f*]-1,6- naphthyridin-8-yl]phenyl}ethanamine;
(1R)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine;
(1R)-1-{4-[3-(1-methyl-1H-imidazol-4-yl)-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl]phenyl}ethanamine;
(1R)-1-[4-(9-phenyl-3-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine;
(1R)-1-[4-(3-imidazo[2,1-b][1,3]thiazol-6-yl-9-phenyl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine;

(1R)-1-[4-(9-phenyl-3-pyrimidin-2-yl[1,2,4]triazolo[3,4-f]-1,6-naphthyridin-8-yl)phenyl]ethanamine;
(1*R*)-1-[4-(9-Phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-1-amine;
2-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine;
2-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]propan-2-amine;
3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl) pyridine;
*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-4-yl-2-furamide;
*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-2-furamide;
*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]-5-pyridin-3-yl-1*H*-pyrrole-3-carboxamide;
2-hydroxy-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;
*tert*-butyl (2-{[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]amino}-2-oxoethyl)carbamate;
4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)morpholine;
2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethanamine;
4-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine;
2,4-dihydroxy-6-(2-{[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyrimidine;
2-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine;
3-(2-{[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-2-oxoethyl)pyridine;
*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-pyrazin-2-ylacetamide;
3-methyl-9-phenyl-8-[4-({[(pyridin-3-ylamino) carbonyl]amino}methyl)phenyl][1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;
2-(2-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;
2-(3-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;
2-(4-hydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;
2-(3,4-dihydroxyphenyl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;
*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl] -2-phenylacetamide;

130

3-methyl-9-phenyl-8-(4-{[(pyridin-3-ylcarbonyl) amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

2-hydroxy-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]benzamide;

2-(4-hydroxyphenyl)-2-methyl-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]propanamide;

methyl 4-{[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]amino}-4-oxobutanoate;

2-hydroxy-*N*-(2-{[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]amino}-2-oxoethyl)benzamide;

*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl] -2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)acetamide;

3-methyl-9-phenyl-8-(4-{[(quinolin-3-ylcarbonyl) amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide;

*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-yl)acetamide;

8-(4-{[(1*H*-benzimidazol-1-ylacetyl)amino]methyl} phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

8-(4-{[(1*H*-benzimidazol-2-ylacetyl)amino]methyl} phenyl)-3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

2-(4-methyl-1,2,5-oxadiazol-3-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;

2-(1*H*-indazol-1-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) benzyl]acetamide;

2-(5,6-dimethyl-4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl)-*N*-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide;

3-methyl-8-[4-({[(6-morpholin-4-ylpyridin-3-yl)carbonyl]amino}methyl)phenyl]-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine;

2-(6-chloropyridin-3-yl)-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]acetamide;

3-cyano-*N*-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)benzyl]propanamide;

3-methyl-9-phenyl-8-(4-{[(3-pyridin-3-yl propanoyl)amino]methyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{[(pyridin-3-ylacetyl)amino]methyl}phenyl)[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine;

9-phenyl-3-pyrazolo[1,5-*a*]pyrimidin-3-yl-8-(4-{[(pyridin-3-ylacetyl)amino]methyl}phenyl)[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridine;

*N*-(3-hydroxy-2,2-dimethylpropyl)-*N*-[4-(3-methyl-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl ) benzyl]acetamide;

*N*-(3-hydroxy-2,2-dimethylpropyl)-*N*-{4-[3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl[1,2,4] triazolo[3,4-*f*]-1,6-naphthyridin-8-yl ] benzyl}-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide;

*tert*-butyl {2-[[4-(3-{[(*tert*-butoxycarbonyl) amino]methyl}-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)benzyl](3-hydroxy-2,2-dimethylpropyl)amino]-2-oxoethyl}carbamate;

3-methyl-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino]cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

3-methyl-9-phenyl-8-(4-{1-[(quinolin-3-yl carbonyl) amino] cyclopropyl}phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

*N*-{1-[4-(3-methyl-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]cyclopropyl}-2-(4-oxoquinazolin-3(4*H*)-yl)acetamide;

3-(1-methyl-1*H*-imidazol-4-yl)-9-phenyl-8-(4-{1-[(pyridin-3-ylacetyl) amino] cyclopropyl} phenyl)[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridine;

*N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}-2-pyridin-3-ylacetamide;

*N*-{(1*R*)-1-[4-(3-methyl-9-phenyl[1,2,4]triazolo [3,4-*f*]-1,6-naphthyridin-8-yl)phenyl]ethyl}acetamide;

*N*-((1*R*)-1-{4-[3-(hydroxymethyl)-9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl]phenyl}ethyl)-2-pyridin-3-ylacetamide;

*N*-{1-methyl-1-[4-(9-phenyl[1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl}acetamide; and

*N*-{1-methyl-1-[4-(3-methyl-9-phenyl [1,2,4]triazolo[3,4-*f*]-1,6-naphthyridin-8-yl) phenyl]ethyl} acetamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

6. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

7. The use of the compound according to Claim 1 for the preparation of a medicament useful in the treatment or prevention of cancer in a mammal in need of such treatment.

SEQUENCE LISTING

<110> Merck & Co., Inc.
Armstrong, Donna
Kelly III, Michael J.
Layton, Mark
Liang, Jun
Li, Yiwei
Hu, Essa H.
Rodzinak, Kevin
Rossi, Mike
Sanderson, Phil
Wang, Jiabing

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TÍTULO DE LA INVENCIÓN

# INHIBIDORES DE LA ACTIVIDAD AKT

## ANTECEDENTES DE LA INVENCIÓN

La presente invención se refiere a compuestos de naftiridina sustituidos los cuales son inhibidores de la actividad de una o más de las isoformas de la serina/treonina quinasa, Akt (también conocida como PKB; en adelante en este documento referida como "Akt"). La presente invención también se refiere a composiciones farmacéuticas que comprenden tales compuestos y a procedimientos de usar los compuestos actuales en el tratamiento de cáncer.

La apoptosis (muerte celular programada) juega papeles esenciales en el desarrollo embrionario y en la patogénesis de diversas enfermedades, tales como enfermedades neuronales degenerativas, enfermedades cardiovasculares y cáncer. El trabajo reciente ha conducido a la identificación de diversos productos génicos pro- y anti-apoptóticos que están implicados en la regulación o ejecución de muerte celular programada. La expresión de genes antiapoptóticos, tales como Bcl2 o Bcl-$x_L$, inhibe la muerte celular apoptótica inducida por diversos estímulos. Por otro lado, la expresión de genes pro-apoptóticos, tales como Bax o Bad, conduce a muerte celular programada (Adams y col. *Science*, 281:1322-1326 (1998)). La ejecución de muerte celular programada está mediada por proteinasas relacionadas con caspasa-, incluyendo caspasa-3, caspasa-7, caspasa-8 y caspasa-9 etc. (Thornberry y col. *Science*, 281:1312-1316 (1998)).

La ruta de quinasa de fosfatidilinositol 3'-OH (PI3K)/Akt parece importante para regular supervivencia celular/muerte celular (Kulik y col. *Mol. Cell. Biol.* 17:1595-1606 (1997); Franke y col., *Cell*, 88:435-437 (1997); Kauffmann-Zeh y col. *Nature* 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek y col., *Science*, 275:661-665 (1997)). Los factores de supervivencia, tales como factor de crecimiento derivado de plaquetas (PDGF), factor de crecimiento nervioso (NGF) y factor de crecimiento-1 similar a insulina (IGF-1), promueven la supervivencia celular bajo diversas afecciones induciendo la actividad de PI3K (Kulik y col. 1997, Hemmings 1997). La PI3K activada conduce a la producción de fosfatidilinositol(3,4,5)-trifosfato (PtdIns(3,4,5)-P3), el cual en cambio se une a, y promueve la activación de, la serina/treonina quinasa Akt, la cual contiene un dominio (PH) de homología de pleckstrina (Franke y col. *Cell*, 81:727-736 (1995); Hemmings *Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi y col., *EMBO J.* 15: 6541-6551 (1996)). Los inhibidores específicos de PI3K o mutantes en Akt negativos dominantes abolen las actividades promotoras de supervivencia de estos factores de crecimiento o citoquinas. Se ha descrito previamente que los inhibidores de PI3K (LY294002 o wortmannina) bloquearon la activación de Akt mediante quinasas que actúan antes. Además, la introducción de PI3K constitutivamente activa o mutantes de Akt promueve la supervivencia celular bajo condiciones en las cuales las células sufren normalmente muerte celular apoptótica (Kulik y col. 1997, Dudek y col. 1997).

Se han identificado tres miembros de la subfamilia de Akt de serina/treonina proteinquinasas reguladas por segundos mensajeros y se han llamado Akt1/ PKBα, Akt2/PKBβ, y Akt3/PKBγ (en adelante en este documento referidas como "Akt1", "Akt2" y "Akt3"), respectivamente. Las isoformas son homólogas, particularmente en regiones que codifican los dominios catalíticos. Las Akts se activan mediante eventos de fosforilación que ocurren en respuesta a señalización de PI3K. La PI3K fosforila fosfolípidos de inositol de membrana, generando los segundos mensajeros fosfatidil-inositol 3,4,5-trisfosfato y fosfatidilinositol 3,4-bisfosfato, los cuales se ha mostrado que unen el dominio PH de Akt. El modelo actual de activación de Akt propone reclutamiento de la enzima a la membrana mediante fosfoinosítidos 3'-fosforilados, donde tiene lugar la fosforilación de los sitios reguladores de Akt mediante las quinasas que actúan antes (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

La fosforilación de Akt1 tiene lugar en dos sitios reguladores, $Thr^{308}$ en el bucle de activación del dominio catalítico y en $Ser^{473}$ cerca del extremo carboxiterminal (D. R. Alessi *y col. EMBO J.* 15:6541-6551 (1996) y R. Meier *y col. J. Biol. Chem.* 272:30491-30497 (1997)). Sitios de fosforilación reguladores equivalentes aparecen en Akt2 y Akt3. La quinasa que actúa antes, la cual fosforila Akt en el sitio de bucle de activación se ha clonado y se ha llamado proteinquinasa 1 dependiente de 3'-fosfoinosítida (PDK1). PDK1 fosforila no sólo Akt, sino también quinasa S6 ribosomal p70, p90RSK, suero y quinasa regulada por glucocorticoides (SGK), y proteinquinasa C. La quinasa que actúa antes que fosforila el sitio regulador de Akt cerca de l extremo carboxiterminal no se ha identificado aún, pero comunicaciones recientes implican un papel para la quinasa unida a integrinas (ILK-1), una serina/treonina proteinquinasa, o autofosforilación.

Análisis de niveles de Akt en tumores humanos mostraron que Akt2 está sobreexpresada en un número significativo de cánceres ováricos (J. Q. Cheng *y col. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271 (1992)) y pancreáticos (J. Q. Cheng *y col. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). De forma similar, se halló que Akt3 se sobreexpresa en líneas celulares de cánceres de mama y próstata (Nakatani y col. *J. Biol. Chem.* 274:21528-21532 (1999).

El supresor de tumores PTEN, una fosfatasa de proteínas y lípidos que retira específicamente el fosfato 3' de PtdIns(3,4,5)-P3, es un regulador negativo de la ruta de PI3K/Akt (Li y col. *Science* 275:1943-1947 (1997), Stambolic y col. *Cell* 95:29-39 (1998), Sun y col. *Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Las mutaciones de la línea germinal de PTEN son responsables de síndromes de cáncer humanos tales como enfermedad de Cowden (Liaw y col. *Nature Genetics* 16:64-67 (1997)). PTEN está eliminado en un gran porcentaje de tumores humanos y las líneas celulares tumorales sin PTEN funcional muestran niveles elevados de Akt activada (Li y col. supra, Guldberg y col. *Cancer Research* 57:3660-3663 (1997), Risinger y col. *Cancer Research* 57:4736-4738 (1997)).

Estas observaciones demuestran que la ruta de PI3K/Akt juega papeles importantes para regular la supervivencia celular o la apoptosis en tumorogénesis.

La inhibición de activación y actividad de Akt puede lograrse inhibiendo PI3K con inhibidores tales como LY294002 y wortmannina. Sin embargo, la inhibición de PI3K tiene el potencial para afectar indiscriminadamente no solamente a todas las tres isozimas de Akt sino también otras moléculas de señalización que contienen dominio PH que son dependientes de PdtIns(3,4,5)-P3, tales como la familia Tec de tirosina quinasas. Además, se ha descrito que Akt se puede activar mediante señales de crecimiento que son independientes de PI3K.

Alternativamente, la Akt se puede inhibir bloqueando la actividad de la quinasa que actúa antes PDK1. No se han descrito inhibidores de PDK1 específicos. Se nuevo, la inhibición de PDK1 daría como resultado inhibición de múltiples proteinquinasas cuyas actividades dependen de PDK1, tales como isoformas de PKC atípicas, SGK, y quinasas S6 (Williams y col. *Curr. Biol.* 10:439-448 (2000).

Es un objetivo de la invención actual proporcionar compuestos novedosos que son inhibidores de Akt.

Es también un objeto de la presente invención proporcionar composiciones farmacéuticas que comprenden los compuestos novedosos que son inhibidores de Akt.

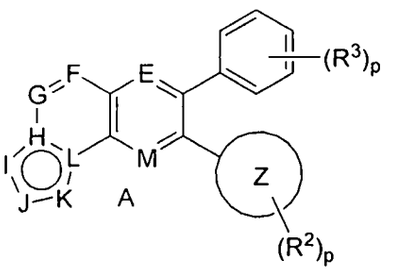
Es también un objeto de la presente invención proporcionar un procedimiento para tratar cáncer que comprende administrar tales inhibidores de actividad Akt.

## SUMARIO DE LA INVENCIÓN

La invención actual estipula compuestos de naftiridina sustituidos que inhiben actividad Akt. En particular, los compuestos descritos inhiben selectivamente una o dos de las isoformas de Akt. La invención también estipula composiciones que comprenden tales compuestos inhibidores y procedimientos para inhibir actividad Akt administrando el compuesto a un paciente en necesidad de tratamiento de cáncer.

## DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los compuestos de la invención actual son útiles en la inhibición de la actividad de la Akt serina/treonina quinasa. En una primera realización de esta invención, los inhibidores de actividad de Akt están ilustrados mediante la Fórmula A:



en la que:

E, F, G, H, I, J, K, L y M se seleccionan independientemente de: C o N, en la que cada E, F, G, H, I, J, K, L y M está opcionalmente sustituido con $R^1$;

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2; p es independientemente 0, 1, 2, 3, 4 ó 5;

El anillo Z se selecciona de: cicloalquilo($C_3$-$C_8$), arilo, heteroarilo y heterociclilo;

$R^1$ se selecciona de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), SH, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^2$ se selecciona independientemente de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), SH, $S(O)_mNR^7R^8$, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^3$ se selecciona independientemente de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquilo($C_1$-$C_6$)-heterociclilo y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^6$ es: $(C=O)_aO_b$alquilo $C_1$-$C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2$-$C_{10}$, alquinilo $C_2$-$C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1$-$C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) o $(C=O)_aO_b$cicloalquilo $C_3$-$C_8$, dichos alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O_a$perfluoroalquilo($C_1$-$C_3$), alquileno($C_0$-$C_6$)-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), cicloalquilo($C_3$-$C_6$), alquileno($C_0$-$C_6$)-arilo, alquileno($C_0$-$C_6$)-heterociclilo, alquileno($C_0$-$C_6$)-$N(R^b)_2$, $C(O)R^a$, alquileno($C_0$-$C_6$)-$CO_2R^a$, C(O)H, y alquileno($C_0$-$C_6$)-$CO_2H$, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$;

$R^7$ y $R^8$ están independientemente seleccionados de: H, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), SH, $SO_2R^a$, y $(C=O)_aNR^b_2$, dichos alquilo, cicloalquilo, arilo, heterociclilo,

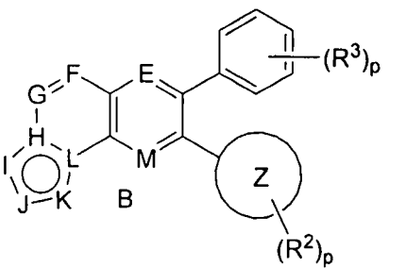
alquenilo, y alquinilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y que opcionalmente contienen, además del nitrógeno, uno o dos heteroátomos adicionales seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^a$ es alquilo($C_1$-$C_6$), cicloalquilo($C_3$-$C_6$), arilo, o heterociclilo; y

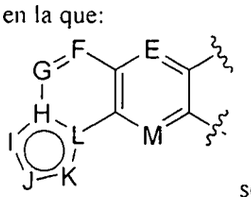
$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), alquilo$(C=O)_aO_b(C_1$-$C_6)$, o $S(O)_mR^a$;

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

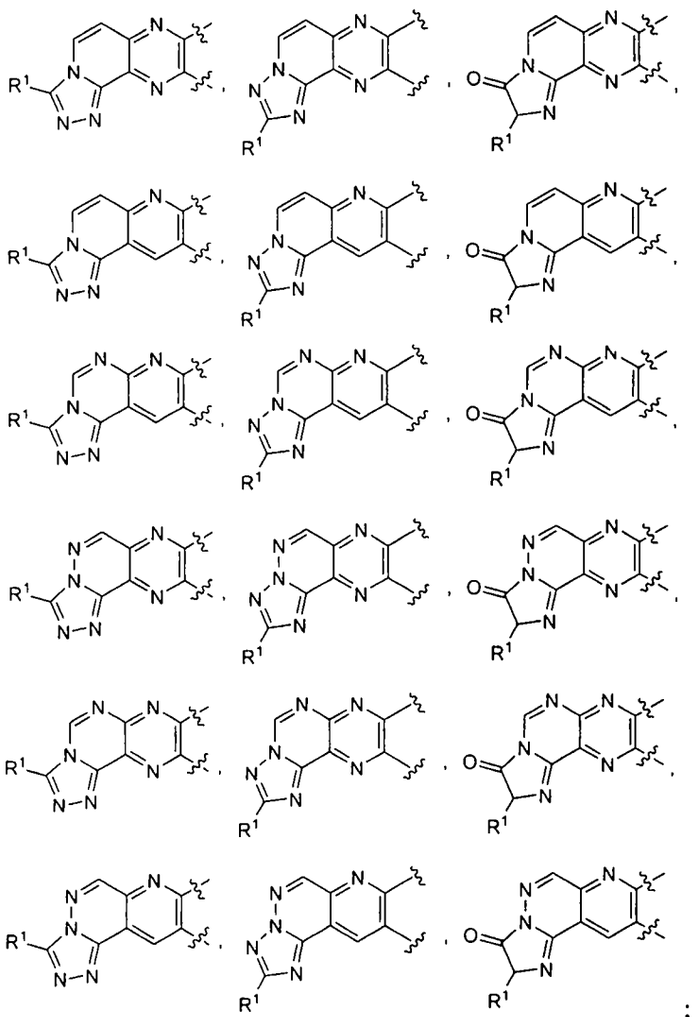
En una segunda realización de esta invención, los inhibidores de actividad de Akt están ilustrados mediante la Fórmula B:




en la que:




se selecciona de:

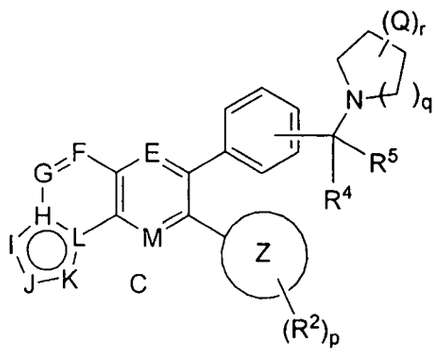


;

$R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

y todos los otros sustituyentes y variables son como se definen en la primera realización; o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una tercera realización de esta invención, los inhibidores de actividad de Akt están ilustrados mediante la Fórmula C:



en la que:

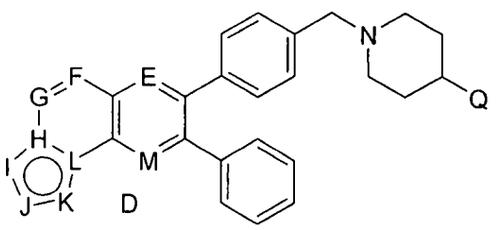
q es 0, 1, 2, 3 ó 4; r es 0, 1, 2, 3, 4 ó 5; t es 2, 3, 4, 5 ó 6;

Q se selecciona independientemente de: oxo, (C=O)aObalquilo($C_1$-$C_{10}$), (C=O)aOb-arilo, (C=O)aObalquenilo($C_2$-$C_{10}$), (C=O)aObalquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, Obperfluoroalquilo($C_1$-$C_6$), (C=O)a$NR^7R^8$, CN, (C=O)aObcicloalquilo($C_3$-$C_8$), S(O)m$NR^7R^8$, SH, S(O)m-alquilo($C_1$-$C_{10}$) y (C=O)aOb-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^4$ y $R^5$ se seleccionan independientemente de: H, alquilo ($C_1$-$C_6$) y perfluoroalquilo($C_1$-$C_6$), o $R^4$ y $R^5$ se combinan para formar -$(CH_2)_t$- en los que uno de los átomos de carbono está opcionalmente reemplazado por un resto seleccionado de O, $S(O)_m$, -$N(R^b)C(O)$-, y -$N(COR^a)$-;

y todos los otros sustituyentes y variables son como se definen en la segunda realización; o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

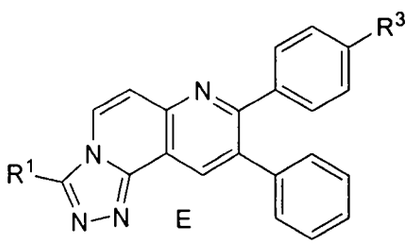
En una cuarta realización los inhibidores de la presente invención están ilustrados mediante la Fórmula D:



en la que:

todos los otros sustituyentes y variables son como se definen en la tercera realización; o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una quinta realización los inhibidores de la presente invención están ilustrados mediante la Fórmula E:



en la que:

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2;

$R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^3$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquilo($C_1$-$C_6$)-heterociclilo y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^6$ es: $(C=O)_aO_b$alquilo $C_1$-$C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2$-$C_{10}$, alquinilo $C_2$-$C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1$-$C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) o $(C=O)_aO_b$cicloalquilo $C_3$-$C_8$, dichos alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O_a$perfluoroalquilo($C_1$-$C_3$), alquileno($C_0$-$C_6$)-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), cicloalquilo($C_3$-$C_6$), alquileno($C_0$-$C_6$)-arilo, alquileno($C_0$-$C_6$)-heterociclilo, alquileno($C_0$-$C_6$)-$N(R^b)_2$, $C(O)R^a$, alquileno($C_0$-$C_6$)-$CO_2R^a$, C(O)H, y alquileno($C_0$-$C_6$)-$CO_2H$, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$;

$R^7$ y $R^8$ están independientemente seleccionados de: H, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), SH, $SO_2R^a$, y $(C=O)_aNR^b_2$, dichos alquilo, cicloalquilo, arilo, heterociclilo, alquenilo, y alquinilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y que opcionalmente contienen,

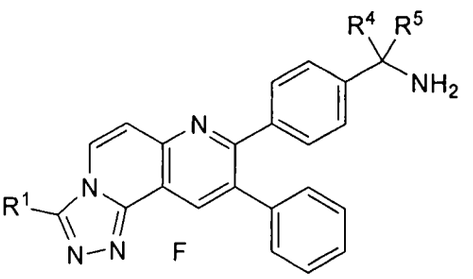
además del nitrógeno, uno o dos heteroátomos adicionales seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^a$ es alquilo($C_1$-$C_6$), cicloalquilo($C_3$-$C_6$), arilo, o heterociclilo; y

$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), alquilo(C=O)$_a$O$_b$($C_1$-$C_6$), o S(O)$_m$$R^a$;

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una sexta realización los inhibidores de la presente invención están ilustrados mediante la Fórmula F:




F

en la que:

$R^4$ y $R^5$ son independientemente: H y alquilo($C_1$-$C_6$), en el que dicho alquilo está opcionalmente sustituido con de uno a tres sustituyentes seleccionados de: OH y halo; y en el que $R^4$ y $R^5$ pueden unirse para formar un cicloalquilo($C_3$-$C_7$); y

todos los otros sustituyentes y variables son como se definen en la quinta realización;

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una séptima realización los inhibidores de la presente invención están ilustrados mediante la Fórmula F:

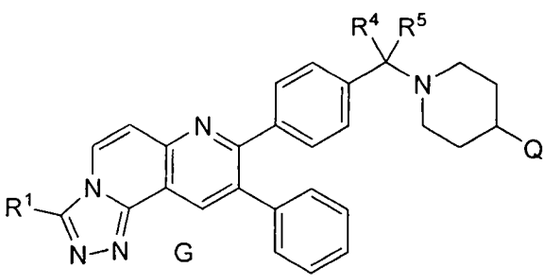
en la que:

$R^1$ se selecciona de: H, $NH_2$, OH y alquilo($C_1$-$C_6$);

$R^4$ y $R^5$ son independientemente: H y alquilo($C_1$-$C_6$);

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una octava realización los inhibidores de la presente invención están ilustrados mediante la Fórmula G:




G

en la que:

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2;

Q se selecciona de: heterociclilo, el cual está opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^4$ y $R^5$ son independientemente: H, alquilo($C_1$-$C_6$), alquenilo($C_1$-$C_6$), alquinilo($C_1$-$C_6$), en el que dicho alquilo está opcionalmente sustituido con de uno a tres sustituyentes seleccionados de: OH y halo; y en los que $R^4$ y $R^5$ se pueden tomar conjuntamente para formar un cicloalquilo($C_3$-$C_7$), en el que dicho cicloalquilo está opcionalmente sustituido con hasta tres sustituyentes seleccionados de $R^6$;

$R^6$ es: $(C=O)_aO_b$alquilo $C_1$-$C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2$-$C_{10}$, alquinilo $C_2$-$C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1$-$C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) o $(C=O)_aO_b$cicloalquilo $C_3$-$C_8$, dichos alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O_a$perfluoroalquilo($C_1$-$C_3$), alquileno($C_0$-$C_6$)-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), cicloalquilo($C_3$-$C_6$), alquileno($C_0$-$C_6$)-arilo, alquileno($C_0$-$C_6$)-heterociclilo, alquileno($C_0$-$C_6$)-$N(R^b)_2$, $C(O)R^a$, alquileno($C_0$-$C_6$)-$CO_2R^a$, C(O)H, y alquileno($C_0$-$C_6$)-$CO_2H$, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$;

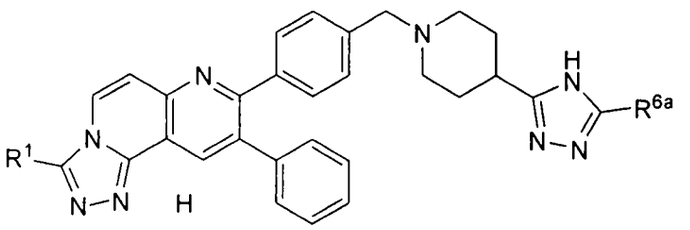
$R^7$ y $R^8$ están independientemente seleccionados de: H, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), SH, $SO_2R^a$, y $(C=O)_aNR^b_2$, dichos alquilo, cicloalquilo, arilo, heterociclilo, alquenilo, y alquinilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y que opcionalmente contienen, además del nitrógeno, uno o dos heteroátomos adicionales seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^a$ es alquilo($C_1$-$C_6$), cicloalquilo($C_3$-$C_6$), arilo, o heterociclilo; y

$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), alquilo$(C=O)_aO_b$($C_1$-$C_6$), o $S(O)_mR^a$;

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

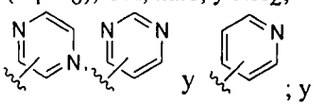
En una novena realización los inhibidores de la presente invención están ilustrados mediante la Fórmula H:



H

en la que:

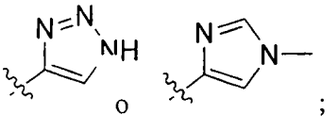
$R^1$ es heterociclilo, dicho heterociclilo está opcionalmente sustituido con de uno a tres sustituyentes seleccionados de: alquilo($C_1$-$C_6$), OH, halo, y $NH_2$;

$R^{6a}$ se selecciona de:  ; y

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una décima realización los inhibidores de la presente invención están ilustrados mediante la Fórmula H:

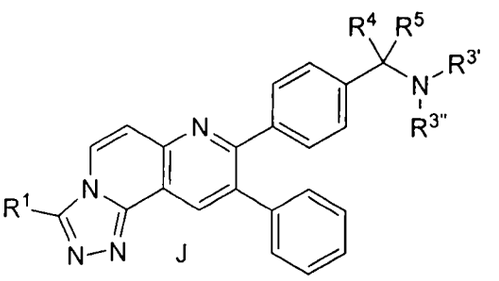
en la que:

$R^1$ se selecciona de:  ;

y todos los otros sustituyentes y variables son como se definen en la novena realización;

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

En una undécima realización los inhibidores de la presente invención están ilustrados mediante la Fórmula J:



J

en la que:

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2;

R1 se selecciona de: $CF_3$, H, oxo, $(C=O)_aO_b$alquilo$(C_1-C_{10})$, $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo$(C_2-C_{10})$, $(C=O)_aO_b$alquinilo(C2-C10), $CO_2H$, halo, OH, $O_b$perfluoroalquilo$(C_1-C_6)$, $(C=O)_nNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo$(C_3-C_8)$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo$(C_1-C_{10})$ y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno a seis sustituyentes seleccionados de $R^6$;

$R^{3'}$ y $R^{3''}$ se selecciona independientemente de: $CF_3$, H, oxo, $(C=O)_aO_b$alquilo$(C_1-C_{10})$, $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo$(C_2-C_{10})$, $(C=O)_aO_b$alquinilo$(C_2-C_{10})$, $CO_2H$, halo, OH, $O_b$perfluoroalquilo$(C_1-C_6)$, $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo$(C_3-C_8)$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo$(C_1-C_{10})$, alquil$(C_1-C_6)$-heterociclilo y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterociclilo están opcionalmente sustituidos con uno a cinco sustituyentes seleccionados de $R^6$; o $R^{3'}$ y $R^{3''}$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar una piperidina o pirrolidina la cual puede estar opcionalmente sustituida con de uno a cinco sustituyentes seleccionados de $R^6$;

$R^4$ y $R^5$ son independientemente: H, alquilo$(C_1-C_6)$, alquenilo$(C_1-C_6)$, alquinilo$(C_1-C_6)$, en el que dicho alquilo está opcionalmente sustituido con de uno a tres sustituyentes seleccionados de: OH y halo; y en los que $R^4$ y $R^5$ se pueden tomar conjuntamente para formar un cicloalquilo$(C_3-C_7)$, en el que dicho cicloalquilo está opcionalmente sustituido con hasta tres sustituyentes seleccionados de $R^6$;

$R^6$ es: $CF_3$, $(C=O)_aO_b$alquilo $C_1-C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2-C_{10}$, alquinilo $C_2-C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1-C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo$(C_1-C_{10})$ o $(C=O)_aO_b$cicloalquilo $C_3-C_8$, dichos alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $CF_3$, $(C=O)_aO_b$alquilo$(C_1-C_{10})$, $O_a$perfluoroalquilo$(C_1-C_3)$, alquileno$(C_0-C_6)$-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo$(C_2-C_{10})$, alquinilo$(C_2-C_{10})$, cicloalquilo$(C_3-C_6)$, alquileno$(C_0-C_6)$-arilo, alquileno$(C_0-C_6)$-heterociclilo, alquileno$(C_0-C_6)$-$N(R_b)^2$, $(C=O)_aNR^b_2$, $C(O)R^a$, alquileno$(C_0-C_6)$-$CO_2R^a$, C(O)H, y alquileno$(C_0-C_6)$-$CO_2H$, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi$(C_1-C_6)$, halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo$(C_1-C_6)$, oxo, y $N(R^b)_2$;

$R^7$ y $R^8$ están independientemente seleccionados de: $CF_3$, H, $(C=O)_aO_b$alquilo(C1-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3-C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo(C2-$C_{10}$), alquinilo($C_2-C_{10}$), SH, $SO_2R_a$, y $(C=O)^aNR^b2$, dichos alquilo, cicloalquilo, arilo, heterociclilo, alquenilo, y alquinilo están opcionalmente sustituidos con uno a cinco sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y que opcionalmente contienen, además del nitrógeno, uno o dos heteroátomos adicionales

seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituido con uno a seis sustituyentes seleccionados de $R^{6n}$;

$R^a$ es alquilo($C_1$-$C_6$), $NR^b_2$, cicloalquilo($C_3$-$C_6$), arilo, o heterociclilo; y

$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), $NH_2$, arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), alquilo(C=O)aOb($C_1$-$C_6$), o $S(O)_mR^a$;

o una sal farmacéuticamente aceptable o un estereoisómero de los mismos.

Compuestos específicos de la presente invención incluyen:

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-amina (**1-4**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-ol (**1-5**);

9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-6**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-tiol (**1-7**);

3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4 ]triazolo[3,4-f]-1,6-naftiridina (**2-2**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-3**);

3-(clorometil)-9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-4**);

3-[(4-metilpiperazin-1-il)metil]-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-5**); y

2-({[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metil}amino)etanol (**2-6**);

o una sal farmacéuticamente aceptable o estereoisómero de los mismos.

Ejemplos de los compuestos de la presente invención incluyen sales de TFA de los siguientes compuestos:

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-amina (**1-4**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-ol (**1-5**);

9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-6**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-tiol (**1-7**);

3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4 ]triazolo[3,4-f]-1,6-naftiridina (**2-2**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-3**);

3-(clorometil)-9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-4**);

3-[(4-metilpiperazin-1-il)metil]-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-5**);

2-({[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metil}amino)etanol (**2-6**);

3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-9**);

3-imidazo[2,1-b][1,3] tiazol-6-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-10**);

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-[1,2,4]triazolo [1,5-a]pirimidin-2-il[1,2,4] triazolo[3,4-f]-1,6-naftiridina (**9-11**);

3-imidazo[1,2-a]piridin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-12**);

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-3**);

5-[({4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}amino)metil]piridin-2-ol (**13-8**);

$N^1$,$N^1$,2,2-tetrametil-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] bencil}propano-1,3-diamina (**13-9**);

$N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(4-hidroxifenil)-beta-alaninamida (**14-6**);

1-[4-(9-fenil-3-piridin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-13**);

4-[3-(1-metil-5-fenil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-41**);

1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1-benzotien-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-42**);

1-{4-[3-(1-isopropil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-43**);

1-{4-[9-fenil-3-(1,4,5,6-tetrahidrociclopenta[c]pirazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-44**);

1-[4-(3-ciclopropil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-48**);

1-{4-[9-fenil-3-(trifluorometil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-49**);

1-{4-[3-(5-metil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-50**);
1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-51**);
4-[3-(1H-indol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-52**);
1-{4-[3-(1-metil-1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-53**);
1-{4-[3-(3-metil-2H-3lambda~5~-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-54**);
4-[3-(6-cloroimidazo[1,2-a]piridin-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-55**);
1-{4-[3-(1H-benzimidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-56**);
4-[3-(5-ciclopropil-4H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-57**);
1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1H-indazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-58**);
4-[9-fenil-3-(3-fenil-1H-pirazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-59**);
1-(4-{9-fenil-3-[3-(trifluorometil)-1H-pirazol-5-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-60**);
1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-61**);
1-{4-[3-(1-bencil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-62**);
1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-63**);
4-[9-fenil-3-(1-fenil-1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-64**);
1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-2-benzotien-1-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-65**);
1-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etano-1,2-diol (**16-68**);
4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}imidazolidin-2-ona (**16-69**);
(2R)-2-amino-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol (**16-70**);
(2R)-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2-(metilamino)etanol (**16-71**);
1-[4-(3-etil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**17-6**);
1-[4-(9-fenil-3-propil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**17-7**);

1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropanamina (**33-5**);
1-{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il] fenil}ciclo propanamina (**33-6**);
1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*] pirimidin-2-il[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil] ciclopropanamina (**33-7**);
*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-4-il-2-furamida (**39-2**);
(3-metil-9-fenil-8-(4-{1-[(piridin-3-ilacetil) amino]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-43**);
3-metil-9-fenil-8-(4-{1-[(quinolin-3-ilcarbonil) amino] ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-44**);
3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{1-[(piridin-3-ilacetil) amino] ciclopropil} fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-46**);
1-[4-(9-etil-2-fenil[1,2,4]triazolo[4',3':1,6]pirido[2,3-*b*]pirazin-3-il)fenil]ciclopropanamina (**42-6**); y
1-[4-(9-etil-3-fenil[1,2,4]triazolo[4',3':1,6]pirido[2,3-*b*]pirazin-2-il)fenil]ciclopropanamina (**42-7**);
o un estereoisómero de los mismos.

Ejemplos de los compuestos de la presente invención incluyen sales de ácido fórmico de los siguientes compuestos:
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-amina (**1-4**); y
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-ol (**1-5**);
o un estereoisómero de los mismos.

Compuestos específicos de la presente invención incluyen:
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-amina (**1-4**);
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-ol (**1-5**);
9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-6**);
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-tiol (**1-7**);
3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4 ]triazolo[3,4-f]-1,6-naftiridina (**2-2**);
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-3**);

3-(clorometil)-9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-4**);

3-[(4-metilpiperazin-1-il)metil]-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-5**);

2-({[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metil}amino)etanol (**2-6**);

8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol (**3-8**);

1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**4-3**);

4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina (**5-3**);

8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**6-2**);

1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**7-4**); y

9-fenil-8-{4-[4-(5-piridin-2-il-4*H*-[1,2,4]triazol-3-il)-piperidin-1-ilmetil]-fenil}-[1,2,4] triazolo[3,4-*f*][1,6]naftiridina (**8-10**)

o una sal farmacéuticamente aceptable o estereoisómero de los mismos.

Ejemplos de los compuestos de la presente invención incluyen sales de HCl de los siguientes compuestos:

8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol (**3-8**);

1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**4-3**);

4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina (**5-3**);

8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**6-2**); y

1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**7-4**);

3-(1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-5**);

[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-il]metilcarbamato de terc-butilo (**9-6**);

[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**9-7**);

5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]-2,4-dihidro-3H-1,2,4-triazol-3-ona (**9-8**);

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,4-triazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-13**);

3-(1H-benzimidazol-6-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-14**);

3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-15**);

3-imidazo[1,2-a]pirimidin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-16**);

5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina (**9-17**);

9-fenil-3-pirazolo[1,5-a]pirimidin-3-il-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-18**);

3-(5-metil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-19**);

3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina (**9-20**);

4-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol (**9-21**);

3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol (**9-22**);

2-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol (**9-23**);

1-{4-[3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida (**9-24**);

1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]piperidina-4-carboxamida (**9-25**);

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-3**);

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-4**);

N-[2-(4-metil-1H-imidazol-2-il)etil]-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo [3,4-f]-1,6-naftiridin-8-il]bencil}amina (**13-5**);

$N^1$-(2-hidroxifenil)-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-beta-alaninamida (**13-6**);

1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida (**13-7**);

3-hidroxi-2,2-dimetil-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-10**);

2-fluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-11**);

2,2-difluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-12**);

2,3-dihidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-13**);

4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil] ciclohexanamina (**13-14**);

4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil] ciclohexanamina (**13-15**);
3-hidroxi-2,2-dimetil-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}propan-1-amina (**13-16**);
3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-17**);
3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-18**);
3-hidroxi-2,2-dimetil-N-{4-[9-fenil-3-(1H-1,2,3-triazol-4-il) [1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] bencil}propan-1-amina (**13-19**);
N-{4-[3-(amoniometil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-3-hidroxi-2,2-dimetilpropan-1-amina (**13-21**);
$N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(2-hidroxifenil)-beta-alaninamida (**14-4**);
(8-{4-[(ciclohexilamino)metil]fenil}-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il)metanol (**14-5**);
[9-fenil-8-(4-{[4-(5-piridin-3-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**14-7**);
1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo [3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida (**14-8**);
1-{4-[3-(1-oxidopiridin-3-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] fenil}metanamina (**16-4**);
1-[4-(3,9-difenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-5**);
1-{4-[3-(4-fluorofenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-6**);
4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}benzonitrilo (**16-7**);
4-(9-fenil-3-pirimidin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina (**16-8**);
1-{4-[3-(1-oxidopiridin-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-9**);
5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}iridina-2-ol (**16-10**);
1-[4-(9-fenil-3-piridin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-11**);
4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina (**16-12**);
1-[4-(9-fenil-3-pirazin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-14**);
1-{4-[9-fenil-3-(1H-1,2,4-triazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**16-15**);
1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-16**);
1-{4-[9-fenil-3-(1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-17**);
1-{4-[3-(3-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-18**);

1-{4-[3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-19**);

1-{4-[3-(1-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-20**);

1-{4-[9-fenil-3-(1,2,5-tiadiazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-21**);

1-{4-[9-fenil-3-(1,2,3-tiadiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-22**);

1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-23**);

{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanamina (**16-24**);

{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol (**16-25**);

1-{4-[9-fenil-3-(2,2,2-trifluoroetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-26**);

1-{4-[9-fenil-3-(1H-tetraazol-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-27**);

8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-carboxamida (**16-28**);

1-{4-[3-(1H-imidazol-1-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**16-29**);

1-(4-{3-[(metilsulfinil)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-30**);

{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}acetonitrilo (**16-31**);

2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol (**16-32**);

N-({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)acetamida (**16-33**);

1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-36**);

1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-38**);

1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-40**);

1-(4-{9-fenil-3-[(2R)-pirrolidin-2-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-44**);

1-(4-{9-fenil-3-[(2S)-pirrolidin-2-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-45**);

4-[3-(1-aminoetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-46**);

1-{4-[3-(1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-47**);

1-{4-[9-fenil-3-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-2-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-66**);

2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}propan-2-amina (**16-67**);

1-{4-[3-(5-etilisoxazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-72**);

5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2,4-dihidro-3H-1,2,4-triazol-3-ona (**16-73**);

6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-4,5-dihidropiridazin-3(2H)-ona (**16-74**);

6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}piridazin-3(2H)-ona (**16-75**);

N-(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)acetamida (**16-76**);

1-{4-[3-(4-fenoxifenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-77**);

1-{4-[3-(1H-benzimidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-78**);

(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)metanol (**16-79**);

4-[3-(4-ciclohexilfenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-80**);

4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-1,3-dihidro-2H-imidazol-2-ona (**16-81**);

1-{4-[3-(4-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**16-82**);

4-[9-fenil-3-(1-propil-1H-imidazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-83**);

1-{4-[3-(1-isopropil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-84**);

1-{4-[3-(1-butil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-85**);

1-[4-(3-imidazo[1,2-a]pirimidin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-86**);

1-(6-metoxipiridin-3-il)-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]metanamina (**17-4**);

N-[(2-metoxipirimidin-5-il)metil]-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amina (**17-5**);

9-fenil-3-(1H-1,2,3-triazol-4-il)-8-(4-{[4-(4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina (**21-4**);

1-{4-[9-fenil-3-(3H-1lambda$^4$,3-tiazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-4**);

1-{4-[9-fenil-3-(1H-pirazol-3-il)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-5**);

1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-6**);

1-{4-[3-(azetidin-1-ilmetil)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**26-3**);

1-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)piperidina-4-carboxamida (**26-4**);

1-{4-[3-(morfolin-4-ilmetil)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**26-5**);

2-[({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)amino]etanol (**26-6**);

1-(4-{3-[(4-metil piperazin-1-il)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**26-7**);

4-[9-fenil-3-(piperazin-1-ilmetil)[1,2,4]triazolo [3,4-f]-1,6-naftiridin-8-il]bencilamina (**26-8**);

N-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)-N-metilamina (**26-9**);

N-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)-N,N-dimetilamina (**26-10**);

3-metil-9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il] metil} fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**31-1**);

1-{4-[9-fenil-3-(5,6,7,8-tetrahidro imidazo[1,2-a]piridin-2-il)[1,2,4] triazolo [3,4-f]-1,6-naftiridin -8-il] fenil}ciclopropanamina (**33-8**);

1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]ciclopropanamina (**33-9**);

1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}ciclopropanamina (**33-10**);

(1R)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil ]etanamina (**34-5**);

(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanamina (**34-6**);

(1*R*)-1-{4-[9-fenil-3-(5-piridin-2-il-1*H*-pirazol-3-il)[1,2,4]triazolo[3,4-*f*]-1,6- naftiridin-8-il]fenil}etanamina (**35-1**);

(1R)-1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina (**35-2**);

(1R)-1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina (**35-3**);

(1R)-1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**35-4**);

(1R)-1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**35-5**);

(1R)-1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**35-6**);

(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-1-amina (**36-1**);

2-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina (**37-4**)

2-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina (**38-1**);

3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil) piridina (**39-1**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-2-furamida (**39-3**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-1*H*-pirrol-3-carboxamida (**39-4**);

4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)morfolina (**39-7**);

2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetanamina (**39-8**);

4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina (**39-9**);

2,4-dihidroxi-6-(2-{[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)pirimidina (**39-10**);

2-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina (**39-11**);

3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina (**39-12**);

3-metil-9-fenil-8-[4-({[(piridin-3-ilamino) carbonil]amino}metil)fenil][1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-14**);

3-metil-9-fenil-8-(4-{[(piridin-3-ilcarbonil) amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-20**);

3-metil-9-fenil-8-(4-{[(quinolin-3-ilcarbonil) amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-26**);

8-(4-{[(1*H*-benzimidazol-1-ilacetil)amino]metil} fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-29**);

8-(4-{[(1*H*-benzimidazol-2-ilacetil)amino]metil} fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-30**);

3-metil-8-[4-({[(6-morfolin-4-ilpiridin-3-il)carbonil]amino}metil)fenil]-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina (**39-34**);

3-metil-9-fenil-8-(4-{[(3-piridin-3-il propanoil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-37**);

3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina (**39-38**);

9-fenil-3-pirazolo[1,5-*a*]pirimidin-3-il-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina (**39-39**);

*N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}-2-piridin-3-ilacetamida (**39-47**); y

*N*-((1*R*)-1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}etil)-2-piridin-3-ilacetamida (**39-49**);

o un estereoisómero de los mismos.

Compuestos específicos adicionales de la presente invención incluyen:

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-amina (**1-4**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-ol (**1-5**);

9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-6**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-tiol (**1-7**);

3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4 ]triazolo[3,4-f]-1,6-naftiridina (**2-2**);

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-3**);

3-(clorometil)-9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-4**);

3-[(4-metilpiperazin-1-il)metil]-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-5**);

2-({[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metil}amino)etanol (**2-6**);

8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol (**3-8**);

1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**4-3**);

4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina (**5-3**);

8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**6-2**);

1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**7-4**);

9-fenil-8-{4-[4-(5-piridin-2-il-4*H*-[1,2,4]triazol-3-il)-piperidin-1-ilmetil]-fenil}-[1,2,4] triazolo[3,4-*f*][1,6]naftiridina (**8-10**);

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-4**);

3-(1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-5**);

[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil) [1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-il]metilcarbamato de terc-butilo (**9-6**);

[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**9-7**);

5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]-2,4-dihidro-3H-1,2,4-triazol-3-ona (**9-8**);

3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-9**);

3-imidazo[2,1-b][1,3] tiazol-6-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-10**);

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-[1,2,4]triazolo [1,5-a]pirimidin-2-il[1,2,4] triazolo[3,4-f]-1,6-naftiridina (**9-11**);

3-imidazo[1,2-a]piridin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-12**);

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,4-triazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-13**);

3-(1H-benzimidazol-6-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-14**);

3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-15**);

3-imidazo[1,2-a]pirimidin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-16**);

5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina (**9-17**);

9-fenil-3-pirazolo[1,5-a]pirimidin-3-il-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-18**);

3-(5-metil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-19**);

3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina (**9-20**);

4-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol (**9-21**);

3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol (**9-22**);

2-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol (**9-23**);

1-{4-[3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida (**9-24**);

1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]piperidina-4-carboxamida (**9-25**);

9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**10-4**);

9-fenil-8-(4-{[4-(5-pirimidin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**11-4**);

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirimidin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**12-1**);

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-3**);

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-4**);

N-[2-(4-metil-1H-imidazol-2-il)etil]-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo [3,4-f]-1,6-naftiridin-8-il]bencil}amina (**13-5**);

$N^1$-(2-hidroxifenil)-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-beta-alaninamida (**13-6**);

1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida (**13-7**);

5-[({4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}amino)metil]piridin-2-ol (**13-8**);

$N^1$,$N^1$,2,2-tetrametil-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] bencil}propano-1,3-diamina (**13-9**);

3-hidroxi-2,2-dimetil-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-10**);

2-fluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-11**);

2,2-difluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-12**);

2,3-dihidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-13**);

4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil] ciclohexanamina (**13-14**);

4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil] ciclohexanamina (**13-15**);

3-hidroxi-2,2-dimetil-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}propan-1-amina (**13-16**);

3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-17**);

3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina (**13-18**);

3-hidroxi-2,2-dimetil-N-{4-[9-fenil-3-(1H-1,2,3-triazol-4-il) [1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] bencil}propan-1-amina (**13-19**);

{[8-(4-{[(3-hidroxi-2,2-dimetilpropil)amino]metil}fenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metil}carbamato de terc-butilo (**13-20**);

N-{4-[3-(ammoniometil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-3-hidroxi-2,2-dimetilpropan-1-amina (**13-21**);

[9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**14-3**);

$N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(2-hidroxifenil)-beta-alaninamida (**14-4**);

(8-{4-[(ciclohexilamino)metil]fenil}-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il)metanol (**14-5**);

$N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(4-hidroxifenil)-beta-alaninamida (**14-6**);

[9-fenil-8-(4-{[4-(5-piridin-3-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**14-7**);

1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo [3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida (**14-8**);

{8-[4-(1-aminociclopropil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol (**15-2**);

1-[4-(9-fenil-3-piridin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-3**);

1-{4-[3-(1-oxidopiridin-3-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] fenil}metanamina (**16-4**);

1-[4-(3,9-difenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-5**);

1-{4-[3-(4-fluorofenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-6**);

4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}benzonitrilo (**16-7**);

4-(9-fenil-3-pirimidin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina (**16-8**);

1-{4-[3-(1-oxidopiridin-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-9**);

5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}iridina-2-ol (**16-10**);

1-[4-(9-fenil-3-piridin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-11**);

4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina (**16-12**);

1-[4-(9-fenil-3-piridin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-13**);

1-[4-(9-fenil-3-pirazin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-14**);

1-{4-[9-fenil-3-(1H-1,2,4-triazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**16-15**);

1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-16**);

1-{4-[9-fenil-3-(1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-17**);

1-{4-[3-(3-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-18**);

1-{4-[3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-19**);

1-{4-[3-(1-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-20**);

1-{4-[9-fenil-3-(1,2,5-tiadiazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-21**);

1-{4-[9-fenil-3-(1,2,3-tiadiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-22**);

1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-23**);

{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanamina (**16-24**);

160

{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol (**16-25**)
1-{4-[9-fenil-3-(2,2,2-trifluoroetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-26**);
1-{4-[9-fenil-3-(1H-tetraazol-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-27**);
8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-carboxamida (**16-28**);
1-{4-[3-(1H-imidazol-1-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**16-29**);
1-(4-{3-[(metilsulfinil)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-30**);
{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}acetonitrilo (**16-31**);
2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol (**16-32**);
N-({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)acetamida (**16-33**);
4-[3-(2-metilimidazo[1,2-a]piridin-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-34**);
1-[4-(9-fenil-3-pirazolo[1,5-a]piridin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-35**);
1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-36**);
1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1,2-benzisoxazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-37**);
1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-38**);
1-{4-[3-(1-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-39**);
1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-40**);
4-[3-(1-metil-5-fenil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-41**);
1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1-benzotien-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-42**);
1-{4-[3-(1-isopropil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-43**);
1-{4-[9-fenil-3-(1,4,5,6-tetrahidrociclopenta[c]pirazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-44**);
1-(4-{9-fenil-3-[(2S)-pirrolidin-2-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-45**);
4-[3-(1-aminoetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-46**);
1-{4-[3-(1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-47**);
1-[4-(3-ciclopropil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-48**);
1-{4-[9-fenil-3-(trifluorometil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-49**);

1-{4-[3-(5-metil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-50**);

1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-51**);

4-[3-(1H-indol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-52**);

1-{4-[3-(1-metil-1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-53**);

1-{4-[3-(3-metil-2H-3lambda$^5$-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-54**);

4-[3-(6-cloroimidazo[1,2-a]piridin-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-55**);

1-{4-[3-(1H-benzimidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-56**);

4-[3-(5-ciclopropil-4H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-57**);

1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1H-indazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-58**);

4-[9-fenil-3-(3-fenil-1H-pirazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-59**);

1-(4-{9-fenil-3-[3-(trifluorometil)-1H-pirazol-5-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**16-60**);

1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-61**);

1-{4-[3-(1-bencil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-62**);

1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-63**);

4-[9-fenil-3-(1-fenil-1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-64**);

1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-2-benzotien-1-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-65**);

1-{4-[9-fenil-3-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-2-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-66**);

2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}propan-2-amina (**16-67**);

1-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etano-1,2-diol (**16-68**);

4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}imidazolidin-2-ona (**16-69**);

(2R)-2-amino-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol (**16-70**);

(2R)-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2-(metilamino)etanol (**16-71**);

1-{4-[3-(5-etilisoxazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-72**);

5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2,4-dihidro-3H-1,2,4-triazol-3-ona (**16-73**);

6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-4,5-dihidropiridazin-3(2H)-ona (**16-74**);

6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}piridazin-3(2H)-ona (**16-75**);

N-(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)acetamida (**16-76**);

1-{4-[3-(4-fenoxifenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-77**);

1-{4-[3-(1H-benzimidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-78**);

(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)metanol (**16-79**);

4-[3-(4-ciclohexilfenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-80**);

4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-1,3-dihidro-2H-imidazol-2-ona (**16-81**);

1-{4-[3-(4-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**16-82**);

4-[9-fenil-3-(1-propil-1H-imidazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**16-83**);

1-{4-[3-(1-isopropil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-84**);

1-{4-[3-(1-butil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**16-85**);

1-[4-(3-imidazo[1,2-a]pirimidin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-86**);

5-({[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amino}metil)piridin-2-ol (**17-3**);

1-(6-metoxipiridin-3-il)-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]metanamina (**17-4**);

N-[(2-metoxipirimidin-5-il)metil]-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amina (**17-5**);

1-[4-(3-etil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**17-6**);

1-[4-(9-fenil-3-propil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**17-7**);

N-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]acetamida (**18-1**);

4-({[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amino}metil)fenol (**19-1**);

1-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il] metil}fenil)[1,2,4]triazolo [3,4-f]-1,6-naftiridin-3-il]metanamina (**20-1**);

9-fenil-3-(1H-1,2,3-triazol-4-il)-8-(4-{[4-(4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina (**21-4**);

1-{4-[3-(1H-Imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-3**);

1-{4-[9-fenil-3-(3H-1lambda$^4$,3-tiazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-4**);

1-{4-[9-fenil-3-(1H-pirazol-3-il)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-5**);

1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-6**);

4-[9-fenil-3-(pirrolidin-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**26-2**);

1-{4-[3-(azetidin-1-ilmetil)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**26-3**);

1-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)piperidina-4-carboxamida (**26-4**);

1-{4-[3-(morfolin-4-ilmetil)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il]fenil} metanamina (**26-5**);

2-[({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)amino]etanol (**26-6**);

1-(4-{3-[(4-metil piperazin-1-il)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina (**26-7**);

4-[9-fenil-3-(piperazin-1-ilmetil)[1,2,4]triazolo [3,4-f]-1,6-naftiridin-8-il]bencilamina (**26-8**);

N-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)-N-metilamina (**26-9**);

N-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)-N,N-dimetilamina (**26-10**);

[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]metanol (**28-1**);

{4-[3-(1-Metil-1*H*-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}metanol (**28-2**);

1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*]pirimidin-2-il[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanol (**29-2**);

9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**30-1**);

3-metil-9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il] metil} fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**31-1**);

9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il) piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-3-ol (**32-1**);

1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropanamina (**33-5**);

1-{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il] fenil}ciclopropanamina (**33-6**);

1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*] pirimidin-2-il[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil] ciclopropanamina (**33-7**);

1-{4-[9-fenil-3-(5,6,7,8-tetrahidro imidazo[1,2-a]piridin-2-il)[1,2,4] triazolo [3,4-f]-1,6-naftiridin -8-il] fenil}ciclopropanamina (**33-8**);

1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]ciclopropanamina (**33-9**);

1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}ciclopropanamina (**33-10**);

(1R)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil ]etanamina (**34-5**);

(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanamina (**34-6**);

(1*R*)-1-{4-[9-fenil-3-(5-piridin-2-il-1*H*-pirazol-3-il)[1,2,4]triazolo[3,4-*f*]-1,6- naftiridin-8-il]fenil}etanamina (**35-1**);

(1R)-1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina (**35-2**);

(1R)-1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina (**35-3**);

(1R)-1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**35-4**);

(1R)-1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**35-5**);

(1R)-1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (**35-6**);

(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-1-amina (**36-1**);

2-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina (**37-4**)

2-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina (**38-1**);

3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil) piridina (**39-1**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-4-il-2-furamida (**39-2**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-2-furamida (**39-3**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-1*H*-pirrol-3-carboxamida (**39-4**);

2-hidroxi-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-5**);

(2-{[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]amino}-2-oxoetil)carbamato de *terc*-butilo (**39-6**);

4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)morfolina (**39-7**);

2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetanamina (**39-8**);

4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina (**39-9**);

2,4-dihidroxi-6-(2-{[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)pirimidina (**39-10**);

2-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina (**39-11**);

3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina (**39-12**);

*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-pirazin-2-ilacetamida (**39-13**);

3-metil-9-fenil-8-[4-({[(piridin-3-ilamino) carbonil]amino}metil)fenil][1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-14**);

2-(2-hidroxifenil)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-15**);

2-(3-hidroxifenil)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-16**);

2-(4-hidroxifenil)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-17**);

2-(3,4-dihidroxifenil)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-18**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil] -2-fenilacetamida (**39-19**);

3-metil-9-fenil-8-(4-{[(piridin-3-ilcarbonil) amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-20**);

2-hidroxi-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]benzamida (**39-21**);

2-(4-hidroxifenil)-2-metil-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]propanamida (**39-22**);

4-{[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-4-oxobutanoato de metilo (**39-23**);

2-hidroxi-*N*-(2-{[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]amino}-2-oxoetil)benzamida (**39-24**);

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil] -2-(5-fenil-4*H*-1,2,4-triazol-3-il)acetamida (**39-25**);

3-metil-9-fenil-8-(4-{[(quinolin-3-ilcarbonil) amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-26**);

*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-(4-oxoquinazolin-3(4*H*)-il)acetamida (**39-27**);

*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-il)acetamida (**39-28**);

8-(4-{[(1*H*-benzimidazol-1-ilacetil)amino]metil} fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-29**);

8-(4-{[(1*H*-benzimidazol-2-ilacetil)amino]metil} fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-30**);

2-(4-metil-1,2,5-oxadiazol-3-il)-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-31**);

2-(1*H*-indazol-1-il)-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida (**39-32**);

2-(5,6-dimetil-4-oxotieno[2,3-*d*]pirimidin-3(4*H*)-il)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida (**39-33**);

3-metil-8-[4-({[(6-morfolin-4-ilpiridin-3-il)carbonil]amino}metil)fenil]-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina (**39-34**);

2-(6-cloropiridin-3-il)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida (**39-35**);

3-ciano-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)bencil]propanamida (**39-36**);

3-metil-9-fenil-8-(4-{[(3-piridin-3-il propanoil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-37**);

3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina (**39-38**);

9-fenil-3-pirazolo[1,5-*a*]pirimidin-3-il-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina (**39-39**);

*N*-(3-hidroxi-2,2-dimetilpropil)-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il ) bencil]acetamida (**39-40**);

*N*-(3-hidroxi-2,2-dimetilpropil)-*N*-{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il ] bencil}-2-(4-oxoquinazolin-3(4*H*)-il)acetamida (**39-41**);

{2-[[4-(3-{[(*terc*-butoxicarbonil) amino]metil}-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil](3-hidroxi-2,2-dimetilpropil)amino]-2-oxoetil}carbamato de *terc*-butilo (**39-42**);

3-metil-9-fenil-8-(4-{1-[(piridin-3-ilacetil) amino]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-43**);

3-metil-9-fenil-8-(4-{1-[(quinolin-3-il carbonil) amino] ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-44**);

*N*-{1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropil}-2-(4-oxoquinazolin-3(4*H*)-il)acetamida (**39-45**);

3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{1-[(piridin-3-ilacetil) amino] ciclopropil} fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**39-46**);

*N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}-2-piridin-3-ilacetamida (**39-47**);

*N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}acetamida (**39-48**);

*N*-((1*R*)-1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}etil)-2-piridin-3-ilacetamida (**39-49**);

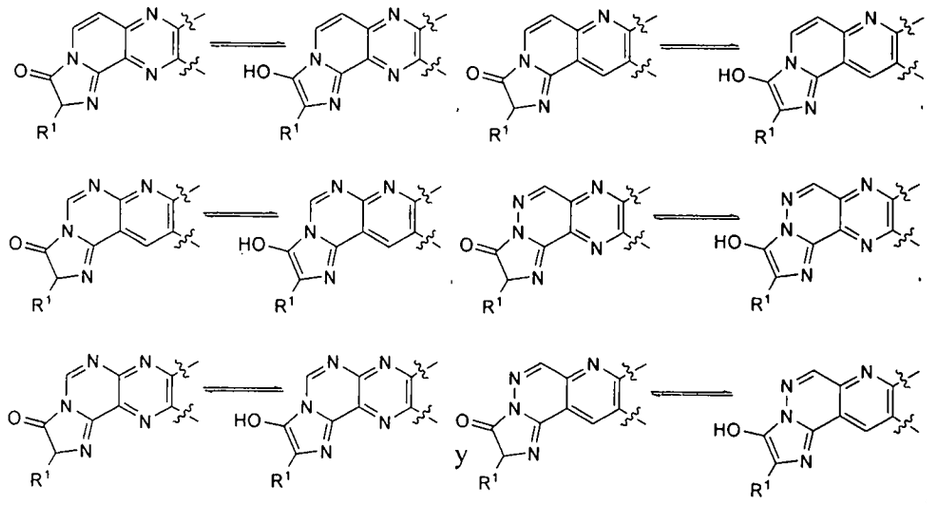
*N*-{1-metil-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) fenil]etil}acetamida (**39-50**); y

*N*-{1-metil-1-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) fenil]etil} acetamida (**39-51**);

o una sal farmacéuticamente aceptable o estereoisómero de los mismos.

El compuesto de la presente invención puede tener centros asimétricos, ejes quirales, y planos quirales (como se describen en: E.L. Eliel y S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, Nueva York, 1994, pages 1119-1190), y aparecen como racematos, mezclas racémicas, y como diastereómeros individuales, con todos los posibles isómeros y mezclas, incluyendo isómeros ópticos, estando todos los estereoisómeros tales incluidos en la presente invención.

Además, los compuestos descritos en el presente documento pueden existir como tautómeros y ambas formas tautómeras se desean para estar comprendidas en el alcance de la invención, incluso aunque sólo se represente una estructura tautómera. Por ejemplo lo siguiente está dentro del alcance de la presente invención:



Los tetrazoles existen como una mezcla de tautómeros 1H/2H. Las formas tautómeras del resto tetrazol están también dentro del alcance de la presente invención.

Cuando cualquier variable (por ejemplo $R^2$, etc.) aparece más de una vez en cualquier constituyente, su definición en cada aparición es independiente en cada una de las apariciones distintas. Además, combinaciones de sustituyentes y variables son permisibles sólo si tales combinaciones dan como resultado compuestos estables. Las líneas trazadas dentro de los sistemas de anillo representan que el enlace indicado puede estar unido a cualquiera de los átomos de anillo sustituibles. Si el sistema de anillo es bicíclico, se desea que el enlace esté unido a cualquiera de los átomos adecuados en cada anillo del resto bicíclico.

Se entiende que uno o más átomos de silicio (Si) se pueden incorporar dentro de los compuestos de la presente invención en lugar de uno o más átomos de carbono por alguien de habilidad ordinaria en la técnica para proporcionar compuestos que sean químicamente estables y que se puedan sintetizar fácilmente mediante técnicas conocidas en la técnica a partir de materiales de partida disponibles. Carbono y silicio difieren en sus radios covalentes conduciendo a diferencias en distancia de enlace y la disposición estérica cuando comparamos enlaces análogos de elemento C y elemento Si. Estas diferencias conducen a cambios sutiles en el tamaño y forma de compuestos que contienen silicio cuando se comparan con carbono. Alguien de habilidad ordinaria en la técnica entendería que las diferencias en tamaño y forma pueden conducir a diferencias sutiles o espectaculares en potencia, solubilidad, carencia de actividad aparte del objetivo, propiedades de empaquetamiento, y así sucesivamente. (Diass, J. O. *y col.* Organometallics (2006) 5:1188-1198; Showell, G.A. y col. Bioorganic & Medicinal Chemistry Letters (2006) 16:2555-2558).

Se entiende que sustituyentes y patrones de sustitución en los compuestos de la presente invención se pueden seleccionar por cualquiera de habilidad ordinaria en la técnica para proporcionar compuestos que son químicamente estables y que se pueden sintetizar fácilmente mediante técnicas conocidas en la técnica, así como aquellos procedimientos expuestos más adelante, a partir de materiales de partida fácilmente disponibles. Si un sustituyente se sustituye por sí mismo con más de un grupo, se entiende que estos grupos múltiples pueden estar en el mismo carbono o en diferentes carbonos, siempre que den como resultado una estructura estable. La frase "opcionalmente sustituido con uno o más sustituyentes" se tomará para ser equivalente a la frase "opcionalmente sustituida con al menos un sustituyente" y en tales casos la realización preferida tendrá de cero a cuatro sustituyentes, y la realización más preferida tendrá de cero a tres sustituyentes.

Como se usa en el presente documento, se desea "alquilo" para incluir tanto grupos hidrocarburo alifáticos ramificados como grupos hidrocarburo alifáticos saturados de cadena lineal que tienen el número de átomos de carbono especificados. Por ejemplo, $C_1$-$C_{10}$, como en "alquilo($C_1$-$C_{10}$)" se define para incluir grupos que tienen 1, 2, 3, 4, 5, 6, 7, 8, 9 ó 10 carbonos en una disposición lineal o ramificada. Por ejemplo, "alquilo($C_1$-$C_{10}$)" incluye específicamente metilo, etilo, *n*-propilo, *i*-propilo, *n*-butilo, *t*-butilo, *i*-butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, y así sucesivamente.

El término "cicloalquilo" significa un grupo hidrocarburo alifático saturado monocíclico que tiene el número especificado de átomos de carbono. Por ejemplo, "cicloalquilo" incluye ciclopropilo, metil-ciclopropilo, 2,2-dimetil-ciclobutilo, 2-etil-ciclopentilo, ciclohexilo, y así sucesivamente.

"Alcoxi" representa bien un grupo alquilo cíclico o bien un grupo alquilo no cíclico del número de átomos de carbono indicado unido por un puente de oxígeno. "Alcoxi" comprende por lo tanto las definiciones de alquilo y cicloalquilo anteriores.

Si no está especificado ningún número de átomos de carbono, el término "alquenilo" se refiere a un radical hidrocarburo no aromático, lineal, ramificado o cíclico, que contiene de 2 a 10

átomos de carbono y al menos un doble enlace carbono carbono. Preferiblemente está presente un doble enlace carbono-carbono, y pueden estar presentes hasta cuatro enlaces dobles carbono-carbono no aromáticos. Así, "alquenilo($C_2$-$C_{10}$)" significa un radical alquenilo que tiene de 2 a 10 átomos de carbono. Grupos alquenilo incluyen etenilo, propenilo, butenilo, 2-metilbutenilo y ciclohexenilo. La parte lineal, ramificada o cíclica del grupo alquenilo puede contener dobles enlaces y puede estar sustituida si está indicado un grupo alquenilo sustituido.

El término "alquinilo" se refiere a un radical hidrocarburo lineal, ramificado o cíclico, que contiene de 2 a 10 átomos de carbono y al menos un triple enlace carbono carbono. Pueden estar presentes hasta tres triples enlaces carbono-carbono. Así, "alquinilo($C_2$-$C_{10}$)" significa un radical alquenilo que tiene de 2 a 10 átomos de carbono. Los grupos alquinilo incluyen etinilo, propinilo, butinilo, 3-metilbutinilo y así sucesivamente. La parte lineal, ramificada o cíclica del grupo alquinilo puede contener triples enlaces y puede estar sustituida si está indicado un grupo alquinilo sustituido.

En ciertos casos, los sustituyentes pueden estar definidos con un intervalo de carbonos que incluyen cero, tal como alquileno ($C_0$-$C_6$)-arilo. Si se toma arilo para ser fenilo, esta definición incluirá fenilo en sí mismo así como -$CH_2$Ph, -$CH_2CH_2$Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, y así sucesivamente.

Como se usa en el presente documento, "arilo" se desea para significar cualquier anillo de carbono monocíclico o bicíclico estable de hasta 7 átomos de carbono en cada anillo, en el que al menos un anillo es aromático. Ejemplos de tales elementos de arilo incluyen fenilo, naftilo, tetrahidro-naftilo, indanilo y bifenilo. En casos donde el sustituyente arilo es bicíclico y un anillo no es aromático, se entiende que el anclaje es por medio del anillo aromático.

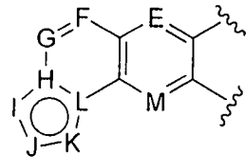
El término heteroarilo, como se usa en el presente documento, representa un anillo monocíclico o bicíclico estable de hasta 7 átomos en cada anillo, en los que al menos un anillo es aromático y contiene de 1 a 4 heteroátomos seleccionados del grupo constituido por O, N y S. Los grupos heteroarilo dentro del alcance de esta definición incluyen pero no se limitan a: acridinilo, carbazolilo, cinnolinilo, quinoxalinilo, pirrazolilo, indolilo, benzotriazolilo, furanilo, tienilo, benzotienilo, benzofuranilo, quinolinilo, isoquinolinilo, oxazolilo, isoxazolilo, indolilo, pirazinilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrahidroquinolina. Como con la definición de heterociclo más adelante, "heteroarilo" se entiende también para incluir el derivado de N-óxido de cualquier heteroarilo que contenga nitrógeno. En casos donde el sustituyente heteroarilo es bicíclico y un anillo no es aromático o no contiene ningún heteroátomo, se entiende que el anclaje es por medio del anillo aromático o por medio del anillo que contiene heteroátomos, respectivamente. Tales restos heteroarilo para sustituyente Q incluyen pero no se limitan a: 2-benzimidazolilo, 2-quinolinilo, 3-quinolinilo, 4-quinolinilo, 1-isoquinolinilo, 3-isoquinolinilo y 4-isoquinolinilo.

El término "heterocíclico" o "heterociclilo" como se usa en el presente documento se desea para significar un heterociclo aromático o no aromático que contiene de 1 a 4 heteroátomos seleccionados del grupo que consta de O, N y S, e incluye grupos bicíclicos. "Heterociclilo" incluye por

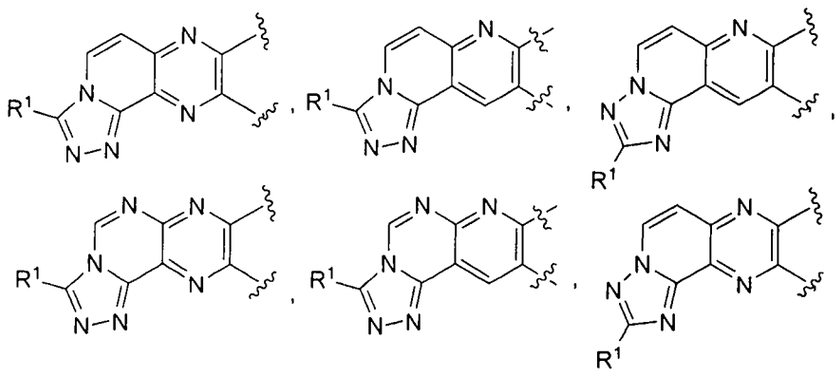
lo tanto los heteroarilos mencionados anteriormente, así como análogos dihidro y tetrahidro de los mismos. Ejemplos adicionales de "heterociclilo" incluyen, pero no se limitan a los siguientes: benzoimidazolilo, benzoimidazolonilo, benzofuranilo, benzofurazanilo, benzopirazolilo, benzotriazolilo, benzotiofenilo, benzoxazolilo, carbazolilo, carbolinilo, cinnolinilo, furanilo, imidazolilo, indolinilo, indolilo, indolazinilo, indazolilo, isobenzofuranilo, isoindolilo, isoquinolilo, isotiazolilo, isoxazolilo, naftpiridinilo, oxadiazolilo, oxazolilo, oxazolina, isoxazolina, oxetanilo, piranilo, pirazinilo, pirazolilo, piridazinilo, piridopiridinilo, piridazinilo, piridilo, pirimidilo, pirrolilo, quinazolinilo, quinolilo, quinoxalinilo, tetrahidropiranilo, tetrazolilo, tetrazolopiridilo, tiadiazolilo, tiazolilo, tienilo, triazolilo, azetidinilo, 1,4-dioxanilo, hexahidroazepinilo, piperazinilo, piperidinilo, piridin-2-onilo, pirrolidinilo, morfolinilo, tiomorfolinilo, dihidrobenzoimidazolilo, dihidrobenzofuranilo, dihidrobenzotiofenilo, dihidrobenzoxazolilo, dihidrofuranilo, dihidroimidazolilo, dihidroindolilo, dihidroisooxazolilo, dihidroisotiazolilo, dihidrooxadiazolilo, dihidrooxazolilo, dihidropirazinilo, dihidropirazolilo, dihidropiridinilo, dihidropirimidinilo, dihidropirrolilo, dihidroquinolinilo, dihidrotetrazolilo, dihidrotiadiazolilo, dihidrotiazolilo, dihidrotienilo, dihidrotriazolilo, dihidroazetidinilo, metilenodioxibenzoilo, tetrahidrofuranilo, y tetrahidrotienilo, y N-óxidos de los mismos. El anclaje de un sustituyente heterociclilo puede tener lugar por medio de un átomo de carbono o por medio de un heteroátomo.

Como se aprecia por aquellos expertos en la técnica, "halo" o "halógeno" como se usa en el presente documento se desea para incluir cloro (Cl), fluoro (F), bromo (Br) y yodo (I).

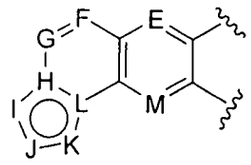
En una realización de Fórmula A, B, C o D, el resto se ilustra mediante la fórmula:



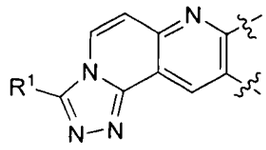

incluye las siguientes estructuras, las cuales se quiere decir que son meramente ilustrativas y no limitantes:



En otra realización de Fórmula A, B, C o D, el resto se ilustra mediante la fórmula:

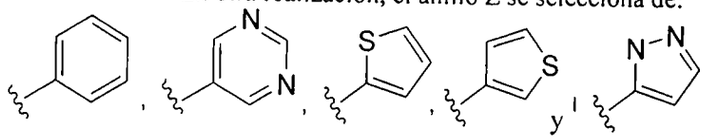


es:



En una realización, el anillo Z se selecciona de: fenilo y heterociclilo.

En otra realización, el anillo Z se selecciona de:



En aún otra realización, el anillo Z es fenilo.

En una realización, p es independientemente 0, 1, 2 ó 3.

En una realización adicional, p es independientemente 0, 1 ó 2.

En otra realización, p es independientemente 1.

En una realización, r es independientemente 0, 1, 2 ó 3.

En una realización adicional, r es 0, 1 ó 2.

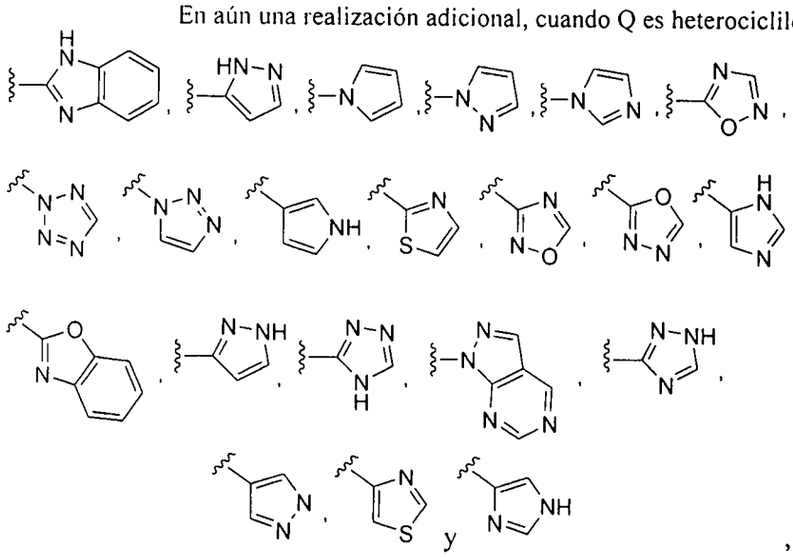
En otra realización, r es 1.

En una realización, Q se selecciona de: benzoimidazolilo, benzoimidazolonilo, benzofuranilo, benzofurazanilo, benzopirazolilo, benzotriazolilo, benzotiofenilo, benzoxazolilo, carbazolilo, carbolinilo, cinnolinilo, furanilo, imidazolilo, indolinilo, indolilo, indolazinilo, indazolilo, isobenzofuranilo, isoindolilo, isoquinolilo, isotiazolilo, isoxazolilo, naftpiridinilo, oxadiazolilo, oxazolilo, oxazolina, isoxazolina, oxetanilo, piranilo, pirazinilo, pirazolilo, piridazinilo, piridopiridinilo, piridazinilo, piridilo, pirimidilo, pirrolilo, quinazolinilo, quinolilo, quinoxalinilo, tetrahidropiranilo, tetrazolilo, tetrazolopiridilo, tiadiazolilo, tiazolilo, tienilo, triazolilo, azetidinilo, 1,4-dioxanilo, hexahidroazepinilo, piperazinilo, piperidinilo, piridin-2-onilo, pirrolidinilo, morfolinilo, tiomorfolinilo, dihidrobenzoimidazolilo, dihidrobenzofuranilo, dihidrobenzotiofenilo, dihidrobenzoxazolilo, dihidrofuranilo, dihidroimidazolilo, dihidroindolilo, dihidroisooxazolilo, dihidroisotiazolilo, dihidrooxadiazolilo, dihidrooxazolilo, dihidropirazinilo, dihidropirazolilo, dihidropiridinilo,

dihidropirimidinilo, dihidropirrolilo, dihidroquinolinilo, dihidrotetrazolilo, dihidrotiadiazolilo, dihidrotiazolilo, dihidrotienilo, dihidrotriazolilo, dihidroazetidinilo, metilenodioxibenzoilo, tetrahidrofuranilo, y tetrahidrotienilo, y N-óxidos de los mismos opcionalmente sustituidos con uno a tres sustituyentes seleccionados de $R^{6a}$. El anclaje de un sustituyente heterociclilo puede tener lugar por medio de un átomo de carbono o por medio de un heteroátomo.

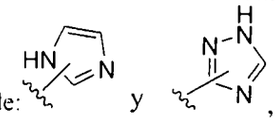
En una realización adicional, Q se selecciona de: 2-azepinona, benzimidazolilo, benzimidazolonilo, 2-diazapinona, imidazolilo, 2-imidazolidinona, indolilo, isoquinolinilo, morfolinilo, piperidilo, piperazinilo, piridilo, pirrolidinilo, 2-piperidinona, 2-pirimidinona, 2-pirolidinona, quinolinilo, tetrazolilo, tetrahidrofurilo, tetrahidroisoquinolinilo, y tienilo, opcionalmente sustituido con de uno a tres sustituyentes seleccionados de $R^{6a}$. El anclaje de un sustituyente heterociclilo puede tener lugar por medio de un átomo de carbono o por medio de un heteroátomo.

En aún una realización adicional, cuando Q es heterociclilo, Q se selecciona de:



, los cuales están opcionalmente sustituidos con de uno a tres sustituyentes seleccionados de $R^{6a}$.

En aún una realización adicional, cuando Q es heterociclilo, Q se selecciona de:



y



, los cuales están opcionalmente sustituidos con un sustituyente seleccionado de $R^{6a}$.

En una realización, $R^1$ se selecciona de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_2NR^7R^8$, SH, $S(O)_2$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con $R^{6n}$.

En otra realización, $R^1$ se selecciona de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $CO_2H$, halo, OH, CN, alcoxi($C_1$-$C_6$), $S(O)_2NR^7R^8$, SH, $S(O)_2$-alquilo($C_1$-$C_{10}$), $O(C=O)$alquilo($C_1$-$C_6$) y $N(R^b)_2$, dicho alquilo está opcionalmente sustituido con $R^{6a}$.

En otra realización, $R^1$ se selecciona de: oxo, $NH_2$, OH, SH, $O_a$alquilo($C_1$-$C_6$), dicho alquilo está opcionalmente sustituido con $R^{6a}$.

En una realización, $R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), , $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_2NR^7R^8$, SH, $S(O)_2$-alquilo($C_1$-$C_{10}$) y $(C=O)_nO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$.

En otra realización, $R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $CO_2H$, halo, OH, CN, alcoxi($C_1$-$C_6$), $S(O)_2NR^7R^8$, SH, $S(O)_2$-alquilo($C_1$-$C_{10}$), $O(C=O)$alquilo($C_1$-$C_6$) y $N(R^b)_2$, dicho alquilo está opcionalmente sustituido con $R^{6a}$.

En otra realización, $R^1$ se selecciona de: oxo, $NH_2$, OH, SH, $O_a$alquilo($C_1$-$C_6$), dicho alquilo está opcionalmente sustituido con $R^{6a}$.

En una realización, $R^2$ se selecciona de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_2NR^7R^8$, $S(O)_2$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterociclilo están opcionalmente sustituidos con $R^b$, OH, alcoxi ($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O(C=O)$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$.

En otra realización, $R^2$ se selecciona de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $CO_2H$, halo, OH, CN, alcoxi($C_1$-$C_6$), $O(C=O)$alquilo($C_1$-$C_6$), alquinilo($C_2$-$C_{10}$) y $N(R^b)_2$, dicho alquilo está opcionalmente sustituido con $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O(C=O)$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$.

En una realización, $R^3$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O^b$-arilo, $O_b$alquenilo($C_2$-$C_{10}$), $O_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquilo($C_1$-$C_6$)-heterociclilo y $(C=O)_nO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$.

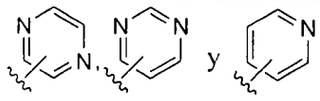
En otra realización, $R^3$ se selecciona de: alquilo($C_1$-$C_{10}$), arilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), halo, $NR^7R^8$, CN, cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquil($C_1$-$C_6$)-heterociclilo y $(C=O)_aO_b$-heterociclilo, dicho alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterociclilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados a partir de $R^6$.

En otra realización, $R^3$ se selecciona de: alquilo($C_1$-$C_{10}$), dicho alquilo será opcionalmente sustituido con uno a tres sustituyentes seleccionados de $NH_2$, OH, oxo y halo.

En otra realización, $R^4$ y $R^5$ son H.

En una realización, cuando Q está sustituido con $R^{6a}$, dicho $R^{6a}$ es heterociclilo opcionalmente sustituido con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$.

En otra realización, cuando Q está sustituido con $R^{6a}$, dicho $R^{6a}$ se selecciona de:


y


opcionalmente sustituidos con 1 a 3 sustituyentes seleccionados a partir de oxo, OH, $N(R^b)_2$, halógeno y $O_a$alquilo($C_1$-$C_6$).

En una realización $R^b$ se selecciona independientemente de H y alquilo($C_1$-$C_6$).

En una realización de Fórmula J, $R^4$ y $R^5$ son independientemente: H y $CH_3$, o $R^4$ y $R^5$ pueden unirse para formar ciclopropilo.

La forma libre de compuestos de Fórmula A está incluida en esta invención, así como las sales y estereoisómeros farmacéuticamente aceptables de los mismos. Algunos de los compuestos específicos aislados ejemplificados en el presente documento son las sales protonadas de compuestos de amina. El término "forma libre" se refiere a los compuestos de amina en forma no salina. Las sales farmacéuticamente aceptables comprendidas no sólo incluyen las sales aisladas ejemplificadas por los compuestos específicos descritos en el presente documento, sino también todas las sales farmacéuticamente aceptables típicas de la forma libre de compuestos de Fórmula A. La forma libre de los compuestos de sal específicos descritos se puede aislar usando técnicas conocidas en la técnica. Por ejemplo, la forma libre se puede regenerar tratando la sal con una solución de base acuosa diluida adecuada tal como NaOH acuoso diluido, carbonato de potasio, amoniaco y bicarbonato de sodio. Las formas libres pueden diferir de sus respectivas formas de sal un tanto en ciertas propiedades físicas, tales como solubilidad en disolventes polares, pero las sales ácidas y básicas son por el contrario farmacéuticamente equivalentes a sus respectivas formas libres para los propósitos de la invención.

Las sales farmacéuticamente aceptables de los presentes compuestos se pueden sintetizar a partir de los compuestos de esta invención los cuales contengan un resto básico o ácido mediante procedimientos químicos convencionales. Generalmente, las sales de los compuestos básicos se preparan bien mediante cromatografía de intercambio iónico o bien haciendo reaccionar la base libre con cantidades estequiométricas o con un exceso del ácido inorgánico u orgánico que forma sal deseado en un disolvente adecuado o en diversas combinaciones de disolventes. De forma similar, las sales de los compuestos ácidos se forman mediante reacciones con la base inorgánica u orgánica apropiada.

Así, sales farmacéuticamente aceptables de los compuestos de esta invención incluyen las sales no tóxicas convencionales de los compuestos de esta invención según se forman haciendo reaccionar un compuesto actual básico con un ácido orgánico o inorgánico. Por ejemplo, sales no tóxicas

convencionales incluyen aquellas derivadas de ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico, nítrico y similares, así como sales preparadas a partir de ácidos orgánicos tales como acético, propiónico, succínico, glicólico, esteárico, láctico, málico, tartárico, cítrico, ascórbico, pamoico, maleico, hidroximaleico, fenilacético, glutámico, benzoico, salicílico, sulfanílico, 2-acetoxi-benzoico, fumárico, toluenosulfónico, metanosulfónico, etanodisulfónico, oxálico, isetiónico, trifluoroacético (TFA) y similares.

Cuando el compuesto de la presente invención es ácido, "sales farmacéuticamente aceptables" adecuadas hace referencia a sales preparadas a partir de bases no tóxicas farmacéuticamente aceptables que incluyen bases inorgánicas y bases orgánicas. Las sales derivadas de bases inorgánicas incluyen de aluminio, de amonio, de calcio, de cobre, férricas, ferrosas, de litio, de magnesio, sales mangánicas, manganosas, de potasio, de sodio, de cinc, y similares. Las sales de amonio, calcio, magnesio, potasio, y sodio son particularmente preferidas. Sales derivadas de bases no tóxicas orgánicas farmacéuticamente aceptables incluyen sales de aminas primarias, secundarias y terciarias, aminas sustituidas que incluyen aminas sustituidas que se dan en la naturaleza, aminas cíclicas y resinas de intercambio iónico básico, tales como arginina, betaína cafeína, colina, N,N$^1$-dibenciletilenediamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilenediamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, isopropilamina, lisina, metilglucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietilamina, trimetilamina tripropilamina, trometamina y similares.

La preparación de las sales farmacéuticamente aceptables descritas anteriormente y otras sales farmacéuticamente aceptables típicas se describe más plenamente por Berg *y col.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

Se notará que los compuestos de la presente invención son potencialmente sales internas o iones bipolares, dado que bajo condiciones fisiológicas un resto ácido desprotonado en el compuesto, tal como un grupo carboxilo, puede ser aniónico, y esta carga electrónica puede equilibrarse después internamente contra la carga catiónica de un resto básico protonado o alquilado, tal como un átomo de nitrógeno cuaternario.

## UTILIDAD

Los compuestos de la presente invención son inhibidores de la actividad de Akt y son así útiles en el tratamiento de cáncer, en particular cánceres asociados con irregularidades en la actividad de Akt y dianas celulares posteriores en activación de Akt. Tales cánceres incluyen, pero no se limitan a, cáncer ovárico, pancreático, de mama y de próstata, así como cánceres (que incluyen glioblastoma) donde está mutado el supresor de tumores PTEN (Cheng y col., *Proc. Natl. Acad. Sci.* (1992) 89:9267-9271; Cheng y col., *Proc. Natl. Acad. Sci.* (1996) 93:3636-3641; Bellacosa y col., *Int. J. Cancer* (1995) 64:280-285; Nakatani y col., *J. Biol. Chem.* (1999) 274:21528-21532; Graff, *Expert. Opin. Ther. Targets* (2002) 6(1):103-113; y Yamada y Araki, *J. Cell Science.* (2001) 114:2375-2382; Mischel y Cloughesy, *Brain Pathol.* (2003) 13(1):52-61).

Los compuestos, composiciones y procedimientos en el presente documento se estiman particularmente útiles para el tratamiento de cáncer. Los cánceres que se pueden tratar mediante los compuestos, composiciones y procedimientos de la invención incluyen, pero no se limitan a: Cardíacos: sarcoma (angiosarcoma, fibrosarcoma, rabdomiosarcoma, liposarcoma), mixoma, rabdomioma, fibroma, lipoma y teratoma; De pulmón: carcinoma broncogénico (de células escamosas, de células pequeñas indiferenciadas, de células grandes indiferenciadas, adenocarcinoma), carcinoma alveolar (bronquiolar), adenoma bronquial, sarcoma, linfoma, hamartoma condromatoso, mesotelioma; Gastrointestinales: de esófago (carcinoma de células escamosas, adenocarcinoma, leiomiosarcoma, linfoma), de estómago (carcinoma, linfoma, leiomiosarcoma), de páncreas (adenocarcinoma ductal, insulinoma, glucagonoma, gastrinoma, tumores carcinoides, vipoma), de intestino delgado (adenocarcinoma, linfoma, tumores carcinoides, sarcoma de Karposi, leiomioma, hemangioma, lipoma, neurofibroma, fibroma), intestino grueso (adenocarcinoma, adenoma tubular, adenoma velloso, hamartoma, leiomioma), de colon, colorrectal, rectal; De tracto genitourinario: de riñón (adenocarcinoma, tumor de Wilm [nefroblastoma], linfoma, leucemia), de vejiga y uretra (carcinoma de células escamosas, carcinoma de células transicionales, adenocarcinoma), de próstata (adenocarcinoma, sarcoma), de testículo (seminoma, teratoma, carcinoma embrionario, teratocarcinoma, coriocarcinoma, sarcoma, carcinoma celular intersticial, fibroma, fibroadenoma, tumores adenomatoides, lipoma); De hígado: hepatoma (carcinoma hepatocelular), colangiocarcinoma, hepatoblastoma, angiosarcoma, adenoma hepatocelular, hemangioma; De hueso: sarcoma osteogénico (osteosarcoma), fibrosarcoma, histiocitoma fibroso maligno, condrosarcoma, sarcoma de Ewing, linfoma maligno (sarcoma de células del retículo), mieloma múltiple, cordoma de tumor de células gigantes malignas, osteocondroma (exostosis osteocartilaginosa), condroma benigno, condroblastoma, condromixofibroma, osteoma osteoide y tumores de células gigantes; De sistema nervioso: de cráneo (osteoma, hemangioma, granuloma, xantoma, enfermedad ósea de Paget), meninges (meningioma, meningiosarcoma, gliomatosis), de cerebro (astrocitoma, meduloblastoma, glioma, ependimoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, tumores congénitos), neurofibroma de la espina dorsal, meningioma, glioma, sarcoma); Ginecológicos: de útero (carcinoma endometrial), de cérvix (carcinoma cervical, displasia cervical pre-tumoral), de ovarios (carcinoma ovárico [cistadenocarcinoma seroso, cistadenocarcinoma mucinoso, carcinoma no clasificado], tumores de células granulosas-tecales, tumores celulares de Sertoli-Leydig, disgerminoma, teratoma maligno), de vulva (carcinoma de células escamosas, carcinoma intraepitelial, adenocarcinoma, fibrosarcoma, melanoma), de vagina (carcinoma de células claras, carcinoma de células escamosas, sarcoma botrioide (rabdomiosarcoma embrionario), de trompas de Falopio (carcinoma); Hematológicos: de sangre (leucemia mieloide [aguda y crónica], leucemia linfoblástica aguda, leucemia linfocítica aguda, enfermedades mieloproliferativas, mieloma múltiple, síndrome mielodisplástico), enfermedad de Hodgkin, linfoma no-Hodgkin [linfoma maligno]; De piel: melanoma maligno, carcinoma de células basales, carcinoma de células escamosas, sarcoma de Karposi, nevos displásicos de lunares, lipoma, angioma, dermatofibroma, queloides, soriasis; y De

glándulas adrenales: neuroblastoma. Así, el término "célula cancerosa" como se proporciona en el presente documento, incluye una célula afligida por una cualquiera de las afecciones identificadas anteriormente.

Los cánceres que se pueden tratar mediante los compuestos, composiciones y procedimientos de la invención incluyen, pero no se limitan a: de mama, de próstata, de colon, colorrectal, de pulmón, de cerebro, testicular, de estómago, de páncreas, de piel, de intestino delgado, de intestino grueso, de garganta, de cabeza y cuello, oral, de hueso, de hígado, de vejiga, de riñón, de tiroides y de sangre.

Los cánceres que pueden ser tratados mediante los compuestos, composiciones y procedimientos de la invención incluyen: de mama, de próstata, de colon, ovárico, colorrectal y de pulmón.

Los cánceres que pueden ser tratados mediante los compuestos, composiciones y procedimientos de la invención incluyen: de mama, de colon (colorrectal) y de pulmón.

Los cánceres que pueden ser tratados mediante los compuestos, composiciones y procedimientos de la invención incluyen: linfoma y leucemia.

La señalización de Akt regula etapas críticas múltiples en angiogénesis. Shiojima y Walsh, *Circ. Res.* (2002) 90:1243-1250. La utilidad de inhibidores de angiogénesis en el tratamiento de cáncer se conoce en la bibliografía, véase J. Rak y col. *Cancer Research*, 55:4575-4580, 1995 y Dredge y col., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966, por ejemplo. El papel de angiogénesis en cancer se ha mostrado en numerosos tipos de cáncer y tejidos: carcinoma de mama (G. Gasparini y A.L. Harris, *J. Clin. Oncol.*, 1995, 13:765-782; M. Toi y col., *Japan. J. Cancer Res.*, 1994, 85:1045-1049); carcinomas de vejiga (A.J. Dickinson y col., *Br. J. Urol.*, 1994, 74:762-766); carcinomas de colon (L.M. Ellis y col., *Surgery*, 1996, 120(5):871-878); y tumores de la cavidad oral (J.K. Williams y col., *Am. J. Surg.*, 1994, 168:373-380). Otros cánceres incluyen, tumores avanzados, leucemia de células vellosas, melanoma, de cabeza y cuello avanzado, de células renales metastático, linfoma no-Hodgkin, de mama metastático, adenocarcinoma de mama, melanoma avanzado, pancreático, gástrico, glioblastoma, pulmón, ovárico, pulmonar no de células pequeñas, de próstata, pulmonar de células pequeñas, carcinoma de células renales, diversos tumores sólidos, mieloma múltiple, de próstata metastático, glioma maligno, cáncer renal, linfoma, enfermedad metastática refractaria, mieloma refractario múltiple, cáncer cervical, sarcoma de Kaposi, glioma anaplásico recurrente, y cáncer de colon metastático (Dredge y col., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). Así, los inhibidores de Akt descritos en la aplicación actual son también útiles en el tratamiento de estos cánceres relacionados con angiogénesis.

Tumores los cuales han sufrido neovascularización muestran un potencial incrementado para metástasis. De hecho, la angiogénesis es esencial para crecimiento tumoral y metástasis. (S.P. Cunningham, y col., *Can. Research*, 61: 3206-3211 (2001)). Los inhibidores de Akt descritos en la presente solicitud son por lo tanto también útiles para impedir o disminuir metástasis de células tumorales.

Adicionalmente está incluido dentro del alcance de la reacción un procedimiento de tratar o prevenir una enfermedad en la cual está implicada la angiogénesis, la cual está comprendida en administrar a un mamífero en necesidad de tal tratamiento una cantidad terapéuticamente efectiva de un compuesto de la presente invención. Las enfermedades neovasculares oculares son un ejemplo de afecciones donde mucho del daño de tejido resultante se puede atribuir a infiltración aberrante de vasos sanguíneos en el ojo (véase documento WO 00/30651, publicado el 2 de junio de 2000). La infiltración indeseable puede activarse mediante retinopatía isquémica, tal como aquella resultante de retinopatía diabética, retinopatía de prematuridad, oclusiones venosas retinales, etc., o mediante enfermedades degenerativas, tales como la neovascularización coroidal observada en degeneración macular relacionada con la edad. La inhibición del crecimiento de los vasos sanguíneos mediante administración de los presentes compuestos prevendría por lo tanto la infiltración de vasos sanguíneos y prevendría o trataría enfermedades donde está implicada la angiogénesis, tales como enfemedades oculares como vascularización retinal, retinopatía diabética, degeneración macular relacionada con la edad, y similares.

Adicionalmente está incluido dentro del alcance de la invención un procedimiento de tratar o prevenir una enfermedad no maligna en la cual está implicada angiogénesis, incluyendo pero no limitada a: enfermedades oculares (tales como, vascularización retinal, retinopatía diabética y degeneración macular relacionada con la edad), aterosclerosis, artritis, soriasis, obesidad y enfermedad de Alzheimer (Dredge y col., *Expert Opin. Biol. Ther.* (2002) 2(8):953-966). En otra realización, un procedimiento de tratar o prevenir un procedimiento de tratar o prevenir una enfermedad en la cual está implicada angiogénesis incluye: enfermedades oculares (tales como, vascularización retinal, retinopatía diabética y degeneración macular relacionada con la edad), aterosclerosis, artritis y psoriasis.

Está incluido adicionalemente dentro del alcance de la invención un procedimiento de tratar trastornos hiperproliferativos, tales como reestenosis, inflamación, enfermedades autoinmunes y alergia/asma.

Está incluido adicionalmente dentro del alcance de la invención actual el uso de los compuestos actuales sobre endoprótesis vasculares recubiertas para el tratamiento y/o prevención de reestenosis (documento de WO03/032809).

Está incluido adicionalmente dentro del alcance de la invención actual el uso de los compuestos actuales para el tratamiento y/o prevención de osteoartritis (documento de WO03/035048).

Está incluido adicionalmente dentro del alcance de la invención un procedimiento de tratar hiperinsulinismo.

Los compuestos de la invención son también útiles en preparar un medicamento que es útil en tratar las enfermedades anteriormente descritas, en particular cáncer.

En una realización de la invención, el compuesto actual es un inhibidor selectivo cuya eficacia inhibidora es dependiente del dominio de PH. En esta realización, el compuesto presenta un decrecimiento en actividad inhibidora *in vitro* o ninguna actividad inhibidora *in vitro* contra proteínas de Akt truncadas que carecen del dominio de PH.

En una realización adicional, el compuesto actual se selecciona del grupo de un inhibidor selectivo de Akt1, un inhibidor selectivo de Akt2 y un inhibidor selectivo tanto de Akt1 como de Akt2.

En otra realización, el compuesto actual se selecciona del grupo de un inhibidor selectivo de Akt1, un inhibidor selectivo de Akt2, un inhibidor selectivo de Akt3 y un inhibidor selectivo de dos de las tres isoformas de Akt.

En otra realización, el compuesto actual es un inhibidor selectivo de todas las tres isoformas de Akt, pero no es un inhibidor de una, dos o todas de tales isoformas de Akt que se han modificado para borrar el dominio PH, la región bisagra o tanto el dominio PH como la región bisagra.

La presente invención se refiere adicionalmente a un procedimiento de inhibir actividad de Akt el cual comprende administrar a un mamífero en necesidad de la misma una cantidad farmacéuticamente efectiva del compuesto actual.

Los compuestos de esta invención se pueden administrar a mamíferos, incluyendo humanos, bien solos o, en combinación con transportadores, excipientes o diluyentes farmacéuticamente aceptables, en una composición farmacéutica, de acuerdo con la práctica farmacéutica estándar. Los compuestos se pueden administrar oralmente o parenteralmente, incluyendo las vías intravenosa, intramuscular, intraperitoneal, subcutánea, rectal y tópica de administración.

Las composiciones farmacéuticas que contienen el ingrediente activo pueden estar en una forma adecuada para el uso oral, por ejemplo, en forma de comprimidos, trociscos, pastillas, suspensiones acuosas o aceitosas, polvos o gránulos dispersables, emulsiones, cápsulas duras o blandas, o jarabes o elixires. Las composiciones destinadas al uso oral pueden prepararse de acuerdo con cualquier procedimiento conocido en la técnica para la fabricación de composiciones farmacéuticas y tales composiciones pueden contener uno o más agentes seleccionados de entre el grupo que consiste en agentes edulcorantes, agentes aromatizantes, agentes colorantes y agentes conservantes para proporcionar preparaciones farmacéuticamente elegantes y apetecibles. Los comprimidos contienen el ingrediente activo mezclado con excipientes no tóxicos farmacéuticamente aceptables los cuales son adecuados para la fabricación de comprimidos. Estos excipientes pueden ser por ejemplo, diluyentes inertes, tales como carbonato cálcico, carbonato sódico, lactosa, fosfato cálcico o fosfato sódico; agentes de granulación y disgregación, por ejemplo, almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina, polivinilpirrolidona o goma arábiga; y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Los comprimidos pueden estar sin recubrir o pueden estar recubiertos mediante técnicas conocidas para enmascarar el sabor desagradable del fármaco o retardar la disgregación y la absorción en el tracto gastrointestinal y proporcionar de este modo una acción mantenida durante un periodo más largo. Por ejemplo, se puede emplear un material enmascarador del sabor soluble en agua tal como hidroxipropilmetil-celulosa o hidroxipropilcelulosa, o un material de retraso temporal tal como etilcelulosa, acetato butirato de celulosa.

Las formulaciones para uso oral también pueden presentarse en forma de cápsulas de gelatina dura en las que el ingrediente activo está mezclado con un diluyente sólido inerte, por ejemplo,

carbonato cálcico, fosfato cálcico o caolín, o en forma de cápsulas de gelatina blanda en las que el ingrediente activo está mezclado con transportador soluble en agua tal como polietilenglicol o un medio aceitoso, por ejemplo aceite de cacahuete, parafina líquida o aceite de oliva.

Las suspensiones acuosas contienen el material activo en mezcla con excipientes adecuados para la fabricación de suspensiones acuosas. Tales excipientes son agentes de suspensión, por ejemplo carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma de tragacanto y goma arábiga; agentes dispersantes o humectantes pueden ser una fosfátida que se da en la naturaleza, por ejemplo lecitina, o productos de condensación de un óxido de alquileno con ácidos grasos, por ejemplo estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetileno-oxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietileno sorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de polietileno sorbitán. Las suspensiones acuosas pueden contener también uno o más conservantes, por ejemplo etilo, o p-hidroxibenzoato de n-propilo, uno o más agentes colorantes, uno o más agentes aromatizantes, y uno o más agentes edulcorantes, tales como sacarosa, sacarina o aspartama.

Las suspensiones oleosas pueden formularse suspendiendo el ingrediente activo en un aceite vegetal, por ejemplo aceite de cacahuete, aceite de oliva, aceite de sésamo o aceite de coco, o en aceite mineral tal como parafina líquida. Las suspensiones oleosas pueden contener un agente espesante, por ejemplo cera de abejas, parafina líquida o alcohol cetílico. Pueden añadirse agentes edulcorantes tales como los que se describen anteriormente, y agentes aromatizantes para proporcionar una preparación oral agradable. Estas composiciones se pueden preservar por la adición de un anti-oxidante tal como hidroxianisol butilado o alfa-tocoferol.

Los polvos dispersables y los gránulos adecuados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el ingrediente activo mezclado con un agente dispersante o humectante, un agente de suspensión y uno o más conservantes. Los agentes dispersantes o humectantes y los agentes de suspensión son ejemplificados por aquellos ya mencionados anteriormente. También puede haber presentes excipientes adicionales, por ejemplo agentes edulcorantes, aromatizantes y colorantes. Estas composiciones pueden conservarse mediante la adicción de antioxidantes tales como ácido ascórbico.

Las composiciones farmacéuticas de la invención pueden estar también en forma de una emulsión de aceite-en-agua. La fase oleosa puede ser un aceite vegetal, por ejemplo aceite de oliva o aceite de cacahuete, o un aceite mineral, por ejemplo parafina líquida o mezclas de éstos. Los agentes emulsionantes adecuados pueden ser fosfátidas que se dan en la naturaleza, por ejemplo lecitina de semilla de soja, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitán, y productos de condensación de los ésteres parciales citados con óxido

de etileno, por ejemplo monooleato de polioxietileno sorbitán. Las emulsiones pueden contener también edulcorantes, agentes aromatizantes, conservantes y antioxidantes.

Los jarabes y elixires pueden formularse con agentes edulcorantes, por ejemplo glicerol, propilenglicol, sorbitol o sacarosa. Tales formulaciones también pueden contener un demulcente, un conservante, agentes aromatizantes y colorantes y antioxidante.

Las composiciones farmacéuticas pueden estar en forma de soluciones acuosas inyectables estériles. Entre los vehículos y disolventes aceptables que pueden emplearse están agua, solución de Ringer y solución de cloruro sódico isotónico.

La preparación inyectable estéril puede ser también una microemulsión estéril inyectable de agua-en-aceite donde el ingrediente activo se disuelve en la fase aceitosa. Por ejemplo, el ingrediente activo puede disolverse primero en una mezcla de aceite de semillas de soja y lecitina. La solución acuosa se introduce después dentro de una mezcla de agua y glicerol y se procesa para formar una microemulsión.

Las soluciones o microemulsiones inyectables se pueden introducir dentro del torrente sanguíneo de un paciente mediante inyección intravenosa rápida local. Alternativamente, puede ser ventajoso administrar la solución o microemulsión en un modo tal como para mantener una concentración circulante constante del compuesto actual. Con el fin de mantener una concentración constante tal, se puede utilizar un dispositivo de administración intravenosa continua. Un ejemplo de un dispositivo tal es la bomba intravenosa Deltec CADD-PLUS™ modelo 5400.

Las composiciones farmacéuticas pueden estar en forma de una suspensión acuosa inyectable estéril o de una suspensión oleaginosa inyectable estéril para administración intramuscular y subcutánea. Esta suspensión puede formularse de acuerdo con la técnica conocida usando aquellos agentes dispersantes o humectantes adecuados y agentes de suspensión que han sido mencionados anteriormente. La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o disolvente, no tóxico parenteralmente aceptable, por ejemplo en forma de una solución en 1,3-butanodiol. Además convencionalmente se emplean aceites fijos estériles en forma de un disolvente o un medio de suspensión. Para este fin pueden emplearse cualquier aceite fijo suave que incluye monoglicéridos o diglicéridos sintéticos. Además, pueden usarse aceites grasos tales como ácido oleico en la preparación de sustancias inyectables.

Los compuestos de Fórmula A se pueden administrar también en forma de supositorios para administración rectal del fármaco. Estas composiciones pueden prepararse mezclando el fármaco con un excipiente no irritante adecuado que sea sólido a las temperaturas habituales pero líquido a la temperatura rectal y que por lo tanto se funda en el recto liberando el fármaco. Tales materiales incluyen mantequilla de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenoglicoles de diversos pesos moleculares y ésteres de ácido graso de polietilenoglicol.

Para uso tópico, se emplean cremas, pomadas, gelatinas, soluciones o suspensiones, etc., que contienen el compuesto de fórmula A. (Para los propósitos de esta solicitud, la aplicación tópica incluirá enjuagues bucales y gárgaras).

Los compuestos para la presente invención se pueden administrar en forma intranasal por medio de uso tópico de vehículos intranasales adecuados y dispositivos de administración, o por medio de vías transdérmicas, usando aquellas formas de parches cutáneos transdérmicos bien conocidos por aquellos de habilidad ordinaria en la técnica. Para administrarse en forma de sistema de administración transdérmico, la administración de dosificación será, por supuesto, continua más que intermitente durante todo el régimen de dosificación. Los compuestos de la presente invención se pueden administrar también como un supositorio empleando bases tales como mantequilla de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenoglicoles de diversos pesos moleculares y ésteres de ácidos grasos de polietilenoglicol.

Cuando una composición de acuerdo con está invención se administra en un sujeto humano, la dosis diaria se determinará normalmente por el médico que receta con la dosificación que varía generalmente de acuerdo con la edad, el peso, y la respuesta del paciente individual, así como con la gravedad de los síntomas del paciente.

El régimen de dosificación que utiliza los compuestos de la invención actual se puede seleccionar de acuerdo con una diversidad de factores incluyendo tipo, especie, edad, peso, sexo y el tipo de cáncer que se esté tratando; la gravedad (es decir, fase) del cáncer a tratarse; la vía de administración; la función renal y hepática del paciente; y el compuesto particular o sal del mismo empleado. Un médico o veterinario de habilidad normal puede determinar y prescribir fácilmente la cantidad efectiva del fármaco requerida para tratar, por ejemplo, para prevenir, inhibir (total o parcialmente) o detener el progreso de la enfermedad.

Por ejemplo, los compuestos de la invención actual se pueden administrar en una dosis diaria total de hasta 10.000 mg. Los compuestos de la invención actual se pueden administrar una vez diariamente (QD), o divididos en múltiples dosis diarias tal como dos veces al día (BID), y tres veces al día (TID). Los compuestos de la invención actual se pueden administrar a una dosificación diaria total de hasta 10.000 mg, por ejemplo, 2.000 mg, 3.000 mg, 4.000 mg, 6.000 mg, 8.000 mg o 10.000 mg, la cual se puede administrar en una dosis diaria o se puede dividir en múltiples dosis diarias como se describe anteriormente.

Por ejemplo, los compuestos de la invención actual se pueden administrar en una dosis diaria total de hasta 1.000 mg. Los compuestos de la invención actual se pueden administrar una vez diariamente (QD), o divididos en múltiples dosis diarias tal como dos veces al día (BID), y tres veces al día (TID). Los compuestos de la invención actual se pueden administrar a una dosificación diaria total de hasta 1.000 mg, por ejemplo, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg o 1.000 mg, la cual se puede administrar en una dosis diaria o se puede dividir en múltiples dosis diarias como se describe anteriormente.

Además, la administración puede ser continua, es decir, cada día, o intermitentemente. Los términos "intermitente" o "intermitentemente" como se usan en el presente documento significan parar y empezar a intervalos bien regulares o bien irregulares. Por ejemplo, la administración intermitente de un compuesto de la invención actual puede ser administración de uno a seis días por semana o puede significar administración en ciclos (por ejemplo administración diaria para de dos a ocho semanas consecutivas, después de un periodo de descanso sin ninguna administración durante hasta una semana) o puede significar administración en días alternos.

Además, los compuestos de la invención actual se pueden administrar de acuerdo con cualquiera de los programas descritos anteriormente, consecutivamente durante unas pocas semanas, seguidas por un periodo de descanso. Por ejemplo, los compuestos de la invención actual se puede administrar de acuerdo con uno cualquiera de los horarios descritos anteriormente de dos a ocho semanas, seguidos por un periodo de descanso de una semana, o dos veces al día a una dosis de 100 - 500 mg durante de tres a cinco días a la semana. En otra realización particular, los compuestos de la invención actual se pueden administrar tres veces diarias durante dos semanas consecutivas, seguidas por una semana de descanso.

Una cualquiera o más de las dosificaciones específicas y programas de dosificación de los compuestos de la invención actual, pueden también ser aplicables a uno o más de los agentes terapéuticos a usarse en el tratamiento de combinación (referido más adelante en el presente documento como el "segundo agente terapéutico").

Además, la dosificación específica y el programa de dosificación específico de este segundo agente terapéutico puede variar adicionalmente, y la dosis óptima, el programa de dosificación y la vía de administración se determinarán en base al segundo agente terapéutico que se está usando.

Por supuesto, la vía de administration de los compuestos de la invención actual es independiente de la vía de administración del segundo agente terapéutico. En una realización, la administración para un compuesto de la invención actual es administración oral. En otra realización, la administración para un compuesto de la invención actual es administración intravenosa. Así, de acuerdo con estas realizaciones, un compuesto de la invención actual se administra oralmente o intravenosamente, y el segundo agente terapéutico se puede administrar oralmente, parenteralmente, intraperitonealmente, intravenosamente, intraarterialmente, transdermalmente, sublingualmente, intramuscularmente, rectalmente, transbucalmente, intranasalmente, liposomalmente, por medio de inhalación, vaginalmente, intraocularmente, por medio de administración local mediante catéter o endoprótesis vascular, subcutáneamente, intraadiposamente, intraarticularmente, intratecalmente, o en una forma de dosificación de liberación lenta.

Además, un compuesto de la invención actual y un segundo agente terapéutico se pueden administrar mediante el mismo modo de administración, es decir ambos agentes administrados por ejemplo oralmente, mediante IV. Sin embargo, también está dentro del alcance de la presente invención administrar un compuesto de la invención actual mediante un modo de administración, por ejemplo oral,

y administrar el segundo agente terapéutico mediante otro modo de administración, por ejemplo IV o cualesquiera otros de los modos de administración descritos anteriormente en el presente documento.

El primer procedimiento de tratamiento, administración de un compuesto de la invención actual, puede tener lugar antes del segundo procedimiento de tratamiento, es decir, el segundo agente terapéutico, después del tratamiento con el segundo agente terapéutico, al mismo tiempo que el tratamiento con el segundo agente terapéutico, o una combinación de los mismos. Por ejemplo, se puede decidir un periodo de tratamiento total para un compuesto de la invención actual. El segundo agente terapéutico se puede administrar antes de la aparición del tratamiento con un compuesto de la invención actual o tras tratamiento con un compuesto de la invención actual. Además, se puede administrar tratamiento anticancerígeno durante el periodo de administración de un compuesto de la invención actual pero no necesita tener lugar durante el periodo de tratamiento entero de un compuesto de la invención actual.

Los compuestos actuales son también útiles en combinación con agentes terapéuticos, quimioterapéuticos y anticancerígenos. Combinaciones de los compuestos actualmente descritos con agentes terapéuticos, quimioterapéuticos y anticancerígenos están dentro del alcance de la invención. Ejemplos de tales agentes se pueden encontrar en *Cancer Principles and Practice of Oncology* por V.T. Devita y S. Hellman (editores), 6ª edición (15 de febrero de 2001), Lippincott Williams & Wilkins Publishers. Una persona de habilidad ordinaria en la técnica sería capaz de distinguir cuales combinaciones de agentes serían útiles en base a las características particulares de los fármacos y el cáncer implicadas. Tales agentes incluyen los siguientes: moduladores de receptor de estrógenos, moduladores de receptor de pirógenos, moduladores de receptor de retinoides, agentes citotóxicos/citostáticos, agentes antiproliferativos, inhibidores de prenil-proteintransferasa, inhibidores de HMG-CoA reductasa y otros inhibidores de angiogénesis, inhibidores de proteasa de VIH, inhibidores de trascriptasa reversa, inhibidores de proliferación celular y señalización de supervivencia, bisfosfonatos, inhibidores de aromatasa, RNAip terapéuticos, inhibidores de γ-secretasa, agentes que interfieren con tirosina quinasas de receptor (RTK) y agentes que interfieren con puntos de control del ciclo celular. Los compuestos actuales son particularmente útiles cuando se coadministran con terapia de radiación.

"Moduladores de receptor de estrógenos" se refiere a compuestos que interfieren con o inhiben la unión de estrógeno al receptor, sin importar el mecanismo. Ejemplos de moduladores de receptor de estrógenos incluyen, pero no se limitan a, tamoxifeno, raloxifeno, idoxifeno, LY353381, LY117081, toremifeno, fulvestrant, 4-[7-(2,2-dimetil-1-oxopropoxi-4-metil-2-[4-[2-(1-piperidinil)etoxi]fenil]-2H-1-benzopiran-3-il]-fenil-2,2-dimetilpropanoato, 4,4'-dihidroxibenzofenona-2,4-dinitrofenil-hidrazona, y SH646.

"Moduladores de receptor de andrógenos" hace referencia a compuestos que interfieren con o inhiben la unión de andrógenos al receptor, sin importar el mecanismo. Ejemplos de

moduladores de receptor de andrógenos incluyen finasteride y otros inhibidores de 5α-reductasa, nilutamida, flutamida, bicalutamida, liarozol, y acetato de abiraterona.

"Moduladores de receptor de retinoides" hace referencia a compuestos que interfieren con o inhiben la unión de retinoides al receptor, sin importar el mecanismo. Ejemplos de tales moduladores de receptor de retinoides incluyen bexaroteno, tretinoína, ácido 13-cis-retinoico, ácido 9-cis-retinoico, α-difluorometilornitina, ILX23-7553, trans-N-(4'-hidroxifenil)retinamida, y N-4-carboxifenilretinamida.

"Agentes citotóxicos/citostáticos" hace referencia a compuestos los cuales causan muerte celular o inhiben ante todo proliferación celular interfiriendo directamente con el funcionamiento de las células o inhibiendo o interfiriendo con miosis celular, incluyendo agentes alquilantes, factores de necrosis tumoral, intercalantes, compuestos activables de hipoxia, agentes inhibidores de microtúbulos/estabilizadores de microtúbulos, inhibidores de quinesinas mitóticas, inhibidores de deacetilasa de histonas, inhibidores de quinasas implicadas en progresión mitótica, inhibidores de quinasas implicadas en factor de crecimiento y rutas de transducción de señales de citoquinas, antimetabolitos, modificadores de respuesta biológica, agentes terapéuticos hormonales/hormonales, factores de crecimiento hematopoyético, agentes terapéuticos dirigidos a anticuerpos monoclonales, inhibidores de topoisomerasa, inhibidores de proteosoma, inhibidores de ubiquitina ligasa, e inhibidores de aurora quinasa.

Ejemplos de agentes citotóxicos/citostáticos incluyen, pero no se limitan a, sertenef, caquectina, ifosfamida, tasonermina, lonidamina, carboplatina, altretamina, prednimustina, dibromodulcitol, ranimustina, fotemustina, nedaplatina, oxaliplatina, temozolomida, heptaplatina, estramustina, tosilato de improsulfano, trofosfamida, nimustina, cloruro de dibrospidio, pumitepa, lobaplatina, satraplatina, profiromicina, cisplatina, irofulven, dexifosfamida, cis-aminadicloro(2-metil-piridina)platino, bencilguanina, glufosfamida, GPX100, tetracloruro de (trans, trans, trans)-bis-mu-(hexano-1,6-diamina)-mu-[diamina-platino(II)]bis[diamina(cloro)platino (II)], diarizidinilspermina, trióxido de arsénico, 1-(11-dodecilamino-10-hidroxiundecil)-3,7-dimetilxantina, zorubicina, idarubicina, daunorubicina, bisantreno, mitoxantrona, pirarrubicina, pinafide, valrubicina, amrubicina, antineoplaston, 3'-deamino-3'-morfolino-13-deoxo-10-hidroxicarminomicina, anamicina, galarrubicina, elinafide, MEN10755, 4-demetoxi-3-deamino-3-aziridinil-4-metilsulfonil-daunorrubicina (véase documento WO 00/50032), inhibidores de Raf quinasa (tal como Bay43-9006) e inhibidores de mTOR (tales como CCI-779 de Wyeth).

Un ejemplo de un compuesto activable de hipoxia es tirapazamina.

Ejemplos de inhibidores de proteosomas incluyen pero no se limitan a lactacistina y MLN-341 (Velcade).

Ejemplos de inhibidores de microtubulos/agentes estabilizadores de microtúbulos incluyen paclitaxel, sulfato de vindesina, 3',4'-didehidro-4'-deoxi-8'-norvincaleucoblastina, docetaxol, rizoxina, dolastatina, isetionato de mivobulina, auristatina, cemadotina, RPR109881, BMS184476,

vinflunina, criptoficina, sulfonamida de 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-metoxifenil)benceno, anhidrovinblastina, N,N-dimetil-L-valil-L-valil-N-metil-L-valil-L-prolil-L-prolina-t-butilamida, TDX258, los epotilones (véase por ejemplo Patentes Estados Unidos N.$^{os}$: 6.284.781 y 6.288.237) y BMS188797. En una realización las epotilonas no se incluyen en los agentes inhibidores de microtúbulos/estabilizadores de microtúbulos.

Algunos ejemplos de inhibidores de topoisomerasa son topotecán, hicaptamina, irinotecán, rubitecán, 6-etoxipropionil-3',4'-O-exo-bencilideno-chartreusina, 9-metoxi-N,N-dimetil-5-nitropirazolo[3,4,5-kl]acridina-2-(6H)propanamina, 1-amino-9-etil-5-fluoro-2,3-dihidro-9-hidroxi-4-metil-1H,12H-benzo[de]pirano[3',4':b,7]-indolizino[1,2b]quinolina-10,13(9H,15H)diona, lurtotecán, 7-[2-(N-isopropilamino)etil]-(20S)camptotecina, BNP1350, BNPI1100, BN80915, BN80942, fosfato de etopósido, tenipósido, sobuzoxano, 2'-dimetilamino-2'-deoxi-etopósido, GL331, N-[2-(dimetilamino)etil]-9-hidroxi-5,6-dimetil-6H-pirido[4,3-b]carbazol-1-carboxamida, asulacrin, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimetilamino)etil]-N-metilamino]etil]-5-[4-hidroxi-3,5-dimetoxifenil]-5,5a,6,8,8a,9-hexohidrofuro(3',4':6,7)nafto(2,3-d)-1,3-dioxol-6-ona, 2,3-(metilenodioxi)-5-metil-7-hidroxi-8-metoxibenzo[c]-fenantridinio, 6,9-bis[(2-aminoetil)amino]benzo[g]isoquinolina-5,10-diona, 5-(3-aminopropilamino)-7,10-dihidroxi-2-(2-hidroxietilaminometil)-6H-pirazolo[4,5,1-de]acridin-6-ona, N-[1-[2(dietilamino)etilamino]-7-metoxi-9-oxo-9H-tioxanto-4-ilmetil]formamida, N-(2-(dimetilamino)etil)acridina-4-carboxamida, 6-[[2-(dimetilamino)etil]amino]-3-hidroxi-7H-indeno[2,1-c]quinolin-7-ona, y dimesna.

Ejemplos de inhibidores de quinesinas mitóticas, y en particular la quinesina mitótica humana KSP, se describen en las Publicaciones WO03/039460, WO03/050064, WO03/050122, WO03/049527, WO03/049679, WO03/049678, WO04/039774, WO03/079973, WO03/099211, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. En una realización los inhibidores de quinesinas mitóticas incluyen, pero no se limitan a inhibidores de KSP, inhibidores de MKLP1, inhibidores de CENP-E, inhibidores de MCAK and inhibidores de Rab6-KIFL.

Ejemplos de "inhibidores de deacetilasa de histonas" incluyen, pero no se limitan a, SAHA, TSA, oxamflatina, PXD101, MG98, ácido valproico y scriptaid. Se puede encontrar referencia adicional a otros inhibidores de deacetilasa de histonas en el siguiente manuscrito; Miller, T.A. y col. *J. Med. Chem.* 46(24): 5097-5116 (2003).

"Inhibidores de quinasas implicadas en progresión mitótica" incluyen, pero no se limitan a, inhibidores de aurora quinasa, inhibidores de quinasas similares a Polo (PLK; en particular inhibidores de PLK-1), inhibidores de bub-1 e inhibidores de bub-R1. Un ejemplo de "inhibidor de aurora quinasa" es VX-680.

"Agentes antiproliferativos" incluyen oligonucleótidos de RNA y DNA antisentido tales como G3139, ODN698, RVASKRAS, GEM231, e INX3001, y antimetabolitos tales como enocitabina, carmofur, tegafur, pentostatina, doxifluridina, trimetrexato, fludarabina, capecitabina, galocitabina,

octofosfato de citarabina, hidrato de fosteabina sodio, raltitrexed, paltitrexid, emitefur, tiazofurina, decitabina, nolatrexed, pemetrexed, nelzarabina, 2'-deoxi-2'-metilidenecitidina, 2'-fluorometileno-2'-deoxicitidina, N-[5-(2,3-dihidro-benzofuril)sulfinil]-N'-(3,4-diclorofenil)urea, N6-[4-deoxi-4-[N2-[2(E),4(E)-tetradecadienoil]glicilamino]-L-glicero-B-L-mano-heptopiranosil]adenina, aplidina, ecteinascidina, troxacitabina, ácido 4-[2-amino-4-oxo-4,6,7,8-tetrahidro-3H-pirimidino[5,4-b][1,4]tiazin-6-il-(S)-etil]-2,5-tienoil-L-glutámico, aminopterina, 5-flurouracilo, alanosina, éster de ácido 11-acetil-8-(carbamoiloximetil)-4-formil-6-metoxi-14-oxa-1,11-diazatetraciclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-il acético, swainsonina, lometrexol, dexrazoxano, metioninasa, 2'-ciano-2'-deoxi-N4-palmitoil-1-B-D-arabinofuranosilcitosina, 3-aminopiridina-2-carboxaldehído tiosemicarbazona y trastuzumab.

Los ejemplos de agentes terapéuticos dirigidos por anticuerpos monoclonales incluyen aquellos agentes terapéuticos los cuales tienen agentes citotóxicos o radioisótopos anclados a un anticuerpo monoclonal específico de célula cancerosa o de célula diana. Ejemplos incluyen Bexxar.

"Inhibidores de HMG-CoA reductasa" hace referencia a inhibidores de 3-hidroxi-3-metilglutaril-CoA reductasa. Ejemplos de inhibidores de HMG-CoA reductasa que se pueden usar incluyen pero no se limitan a lovastatina (MEVACOR®; véanse las Patentes de los Estados Unidos N.°s: 4.231.938, 4.294.926 y 4.319.039), simvastatina (ZOCOR®; véanse Patentes de los Estados Unidos N.°s: 4.444.784, 4.820.850 y 4.916.239), pravastatina (PRAVACHOL®; véanse Patentes de los Estados Unidos N.°s: 4.346.227, 4.537.859, 4.410.629, 5.030.447 y 5.180.589), fluvastatina (LESCOL®; véanse Patentes de los Estados Unidos N.°s: 5.354.772, 4.911.165, 4.929.437, 5.189.164, 5.118.853, 5.290.946 y 5.356.896), atorvastatina (LIPITOR®; véanse Patentes de los Estados Unidos N.°s: 5.273.995, 4.681.893, 5.489.691 y 5.342.952) y cerivastatina (también conocida como rivastatina y BAYCHOL®; véase la Patente de los Estados Unidos N.°: 5.177.080). Las fórmulas estructurales de estos inhibidores de HMG-CoA reductasa e inhibidores adicionales de HMG-CoA reductasa que se pueden usar en los procedimientos actuales se describen en la página 87 de M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) y en Patentes de los Estados Unidos N.°s: 4.782.084 y 4.885.314. El término inhibidor de HMG-CoA reductasa como se usa en el presente documento incluye todas las formas de lactona y formas de ácido abiertas farmacéuticamente aceptables (es decir, donde el anillo de lactona está abierto para formar el ácido libre) así como formas sal y éster de compuestos los cuales tienen actividad inhibidora de HMG-CoA reductasa, y por ello el uso de tales formas sales, ésteres, de ácido abierto y de lactona están incluidas en el alcance de esta invención.

"Inhibidor de prenil-proteintransferasa" hace referencia a un compuesto el cual inhibe una cualquiera o cualquier combinación de las enzimas prenil-proteintransferasas, que incluyen farnesil-proteintransferase (FPTasa), geranilgeranil-proteintransferasa de tipo I (GGPTasa-I), y geranilgeranil-proteintransferasa de tipo II (GGPTasa-II, también llamada GGPTasa de Rab).

Ejemplos de inhibidores de prenil-proteintransferasa se pueden encontrar en las siguientes publicaciones y patentes: documentos WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, Patente de los EE.UU. 5.420.45,

Patente de los EE.UU. 5.523.430, Patente de los EE.UU. 5.532.359, Patente de los EE.UU. 5.510.510, Patente de los EE.UU. 5.589.485, Patente de los EE.UU. 5.602.098, Publicación de Patente Europea 0 618 221, Publicación de Patente Europea 0 675 112, Publicación de Patente Europea 0 604 181, Publicación de Patente Europea 0 696 593, documentos WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, Patente de los EE.UU. 5.661.152, documentos WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, Patente de los EE.UU. 5.571.792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, y Patente de los EE.UU. 5.532.359. Para un ejemplo del papel de un inhibidor de proteína prenil-transferasa en angiogénesis véase *European J. of Cancer*, vol. 35, N°. 9, pp.1394-1401 (1999).

"Inhibidores de angiogenesis" hace referencia a compuestos que inhiben la formación de nuevos vasos sanguíneos, sin importar el mecanismo. Los ejemplos de inhibidores de angiogenesis incluyen, pero no se limitan a, inhibidores de tirosina quinasas, tales como inhibidores de los receptores de tirosina quinasas Flt-1 (VEGFR1) y Flk-1/KDR (VEGFR2), inhibidores de factores de crecimiento derivados de epidermis, derivados de fibroblastos, o derivados de plaquetas, inhibidores de MMP (metaloproteasa de matriz), bloqueantes de integrinas, interferon-α, interleucina-12, polisulfato de pentosán, inhibidores de ciclooxigenasa, que incluyen antiinflamatorios no esteroídicos (NSAID) como aspirina e ibuprofeno así como inhibidores de ciclooxigenasa-2 selectivos como celecoxib y rofecoxib (*PNAS*, vol. 89, p. 7384 (1992); *JNCI*, vol. 69, p. 475 (1982); *Arch. Opthalmol.*, vol. 108, p.573 (1990); *Anat. Rec.*, vol. 238, p. 68 (1994); *FEBS Letters*, vol. 372, p. 83 (1995); *Clin, Orthop.* vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, vol. 75, p. 105 (1997); *Cancer Res.*, vol. 57, p. 1625 (1997); *Cell*, vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, vol. 2, p. 715 (1998); *J. Biol. Chem.*, vol. 274, p. 9116 (1999)), antiinflamatorios esteroídicos (tales como corticosteroides, mineralocorticoides, dexametasona, prednisona, prednisolona, metilpred, betametasona), carboxiamidotriazol, combretastatina A-4, esqualamina, 6-O-cloroacetil-carbonil)-fumagilol, talidomida, angiostatina, troponina-1, antagonistas de angiotensina II (véase Fernández y col., *J. Lab. Clin. Med.* 105:141-145 (1985)), y anticuerpos contra VEGF (véase, *Nature Biotechnology*, vol. 17, páginas 963-968 (October 1999); Kim y col., *Nature*, *362*, 841-844 (1993); documento WO 00/44777; y documento WO 00/61186).

Otros agentes terapéuticos que modulan o inhiben angiogénesis y se pueden usar también en combinación con los compuestos de la invención actual incluyen agentes que modulan o inhiben los sistemas de coagulación y fibrinolisis (véase revisión en *Clin. Chem. La. Med.* 38:679-692 (2000)). Los ejemplos de tales agentes que modulan o inhiben las rutas de coagulación y fibrinolisis incluyen, pero no

se limitan a, heparina (véase *Thromb. Haemost.* 80:10-23 (1998)), heparinas de bajo peso molecular e inhibidores de carboxipeptidasa U (también conocidos como inhibidores de inhibidor de fibrinolilis activable por trombina activa [TAFIa]) (véase *Thrombosis Res.* 101:329-354 (2001)). Los inhibidores de TAFIa se han descrito en los documentos de los Estados Unidos con N°s. de Serie: 60/310,927 (presentado el 8 de agosto de 2001) y 60/349,925 (presentado el 18 de enero de 2002).

"Agentes que interfieren con puntos de control del ciclo celular" hace referencia a compuestos que inhiben proteinquinasas que transducen señales de puntos de control del ciclo celular, sensibilizando de este modo a la célula cancerosa frente a los agentes que dañan el DNA. Tales agentes incluyen inhibidores de ATR, ATM, las quinasas CHK11 y CHK12 e inhibidores de quinasas cdk y cdc y se ejemplifican específicamente mediante 7-hidroxistaurosporina, flavopiridol, CYC202 (Cyclacel) y BMS-387032.

"Agentes que interfieren con tirosina quinasas receptoras (RTK)" hace referencia a compuestos que inhiben RTK y por lo tanto a mecanismos implicados en oncogénesis y progresión de tumores. Tales agentes incluyen inhibidores de c-Kit, Eph, PDGF, Flt3 y c-Met. Agentes adicionales incluyen inhibidores de RTK como se describen por Bume-Jensen y Hunter, *Nature*, 411:355-365, 2001.

"Inhibidores de proliferación celular y ruta de señalización de supervivencia" hace referencia a compuestos que inhiben cascadas de transducción de señales más adelante en la secuencia de receptores de superficie celular. Tales agentes incluyen inhibidores de serina/treonina quinasas (incluyendo pero no limitados a inhibidores de Akt tal como se describe en documentos WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469), inhibidores de Raf quinasa (por ejemplo BAY-43-9006 ), inhibidores de MEK (por ejemplo CI-1040 y PD-098059), inhibidores de mTOR (por ejemplo Wyeth CCI-779), y inhibidores de PI3K (por ejemplo LY294002).

Como se describe anteriormente, las combinaciones con NSAID se refieren al uso de NSAID los cuales son agentes inhibidores de COX-2 potentes. Para propósitos de esta especificación un NSAID es potente si posee una $CI_{50}$ para la inhibición de COX-2 de 1μM o menos como se mide mediante ensayos celulares o microsomales.

La invención también comprende combinaciones con NSAID las cuales son inhibidores de COX-2 selectivas. Para los propósitos de esta solicitud NSAID los cuales son inhibidores selectivos de COX-2 se definen como aquellos los cuales poseen una especificidad para inhibir COX-2 por encima de COX-1 de al menos 100 veces según se mide mediante la razón de la $CI_{50}$ para COX-2 sobre la $CI_{50}$ para COX-1 evaluadas mediante ensayos celulares o microsomales. Tales compuestos incluyen, pero no se limitan a aquellos descritos en Patente de los Estados Unidos 5.474.995, Patente de los Estados Unidos 5.861.419, Patente de los Estados Unidos 6.001.843, Patente de los Estados Unidos 6.020.343, Patente de los Estados Unidos 5.409.944, Patente de los Estados Unidos 5.436.265, Patente de los

190

Estados Unidos 5.536.752, Patente de los Estados Unidos 5.550.142, Patente de los Estados Unidos 5.604.260, Patente de los Estados Unidos 5.698.584, Patente de los Estados Unidos 5.710.140, documento WO 94/15932, Patente de los Estados Unidos 5.344.991, Patente de los Estados Unidos 5.134.142, Patente de los Estados Unidos 5.380.738, Patente de los Estados Unidos 5.393.790, Patente de los Estados Unidos 5.466.823, Patente de los Estados Unidos 5.633.272 y Patente de los Estados Unidos 5.932.598, todas las cuales se incorporan por la presente mediante referencia.

Los inhibidores de COX-2 que son particularmente útiles en el documento actual son: 3-fenil-4-(4-(metilsulfinil)fenil)-2-(*5H*)-furanona; y 5-cloro-3-(4-metilsulfinil)fenil-2-(2-metil-5-piridinil)piridina; o una sal farmacéuticamente aceptable de los mismos.

Los compuestos que se han descrito como inhibidores específicos de COX-2 y son por lo tanto útiles en la presente invención incluyen, pero no se limitan a, los siguientes: parecoxib, BEXTRA® y CELEBREX® o una farmacéuticamente aceptable de los mismos.

Otros ejemplos de inhibidores de angiogénesis incluyen, pero no se limitan a, endostatina, ucraina, ranpirnasa, IM862, 5-metoxi-4-[2-metil-3-(3-metil-2-butenil)oxiranil]-1-oxaspiro[2,5]oct-6-il(cloroacetil)carbamato, acetildinanalina, 5-amino-1-[[3,5-dicloro-4-(4-clorobenzoil)fenil]metil]-1H-1,2,3-triazol-4-carboxamida, CM101, escualamina, combretastatina, RPI4610, NX31838, fosfato de manopentanosa, 7,7-(carbonil-bis[imino-N-metil-4,2-pirrolocarbonilimino[N-metil-4,2-pirrolo]-carbonilimino]-bis-(1,3-naftalenodisulfonato), y 3-[(2,4-dimetilpirrol-5-il)metileno]-2-indolinona (SU5416).

Como se usa anteriormente, "bloqueantes de integrinas" se refiere a compuestos los cuales antagonizan, inhiben o contrarrestan selectivamente la unión de un ligando fisiológico a la integrina $\alpha_v\beta_3$, a compuestos los cuales antagonizan, inhiben o contrarrestan selectivamente la unión de un ligando fisiológico a la integrina $\alpha v\beta 5$, a compuestos los cuales antagonizan, inhiben o contrarrestan selectivamente la unión de un ligando fisiológico tanto a la integrina $\alpha_v\beta_3$ como a la integrina $\alpha_v\beta_5$, y a compuestos los cuales antagonizan, inhiben o contrarrestan la actividad de la(s) integrina(s) particular(es) expresada(s) en células endoteliales capilares. El término también se refiere a antagonistas de las integrinas $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ y $\alpha_6\beta_4$. El término también se refiere a antagonistas de cualquier combinación de las integrinas $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ y $\alpha_6\beta_4$.

Algunos ejemplos específicos de inhibidores de tirosina quinasas incluyen N-(trifluorometilfenil)-5-metilisoxazol-4-carboxamida, 3-[(2,4-dimetilpirrol-5-il)metilidenil]indolin-2-ona, 17-(alilamino)-17-demetoxigeldanamicina, 4-(3-cloro-4-fluorofenilamino)-7-metoxi-6-[3-(4-morfolinil)propoxil]quinazolina, N-(3-etinilfenil)-6,7-bis(2-metoxietoxi)-4-quinazolinamina, BIBX1382, 2,3,9,10,11,12-hexahidro-10-(hidroximetil)-10-hidroxi-9-metil-9,12-epoxi-1H-diindolo[1,2,3-fg:3',2',1'-kl]pirrolo[3,4-i][1,6]benzodiazocin-1-ona, SH268, genisteína, STI571, CEP2563, 4-(3-clorofenilamino)-5,6-dimetil-7H-pirrolo[2,3-d]pirimidinametanosulfonato, 4-(3-bromo-4-hidroxifenil)amino-6,7-

dimetoxiquinazolina, 4-(4'-hidroxifenil)amino-6,7-dimetoxiquinazolina, SU6668, STI571A, N-4-clorofenil-4-(4-piridilmetil)-1-ftalazinamina, y EMD121974.

Están también comprendidas en los procedimientos actuales combinaciones con compuestos distintos de compuestos anticancerígenos. Por ejemplo, combinaciones de los compuestos actualmente reivindicados con agonistas de PPAR-γ (es decir, PPAR-gamma) y agonistas de PPAR-δ (es decir, PPAR-delta) son útiles en el tratamiento de ciertas malignidades. PPAR-γ y PPAR-δ son los receptores activados con proliferador de peroxisoma nuclear γ y δ. La expresión de PPAR-γ en células endoteliales y su implicación en angiogénesis se ha comunicado en la bibliografía (véanse los documentos *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000, 41: 2309-2317). Más recientemente, agonistas de PPAR-γ han estado mostrando inhibir la respuesta angiogénica a VEGF *in vitro*; tanto maleato de troglitazona como maleato de rosiglitazona inhiben el desarrollo de neovascularización retinal en ratones. (*Arch. Ophthamol.* 2001; 119:709-717). Ejemplos de agonistas de PPAR-γ y agonistas de PPAR-γ/α incluyen, pero no se limitan a, tiazolidinedionas (tales como DRF2725, CS-011, troglitazona, rosiglitazona, y pioglitazona), fenofibrato, gemfibrozil, clofibrato, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, ácido 2-[(5,7-dipropil-3-trifluorometil-1,2-benzisoxazol-6-il)oxi]-2-metilpropiónico (descritos en USSN 09/782.856), y ácido 2(R)-7-(3-(2-cloro-4-(4-fluorofenoxi) fenoxi)propoxi)-2-etilcromano-2-carboxílico (descrito en USSN 60/235.708 y 60/244.697).

Otra realización de la invención actual es el uso de los compuestos actualmente discutidos en combinación con terapia génica para el tratamiento de cáncer. Para una visión general de las estrategias genéticas para tratar el cáncer véase Hall y col. (*Am. J. Hum. Genet.* 61:785-789, 1997) y Kufe y col. (Cancer Medicine, 5ª edición, páginas 876-889, BC Decker, Hamilton 2000). Se puede usar la terapia génica para administrar cualquier gen supresor de tumores. Ejemplos de tales genes incluyen, pero no se limitan a, p53, el cual se puede administrar por medio de transferencia génica mediada por virus recombinante (véase Patente de los EE.UU. 6.069.134, por ejemplo), un antagonista de uPA/uPAR ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," Gene Therapy, agosto de 1998; 5(8): 1105-13), e interferon gamma (*J. Immunol.* 2000;164:217-222).

Los compuestos de la invención actual se puede administrar también en combinación con un inhibidor de resistencia multifármaco (MDR) inherente, en particular MDR asociada con niveles altos de expresión de proteínas transportadoras. Tales inhibidores de MDR incluyen inhibidores de p-glicoproteína (P-gp), tales como LY335979, XR9576, OC144-093, R101922, VX853 y PSC833 (valspodar).

Un compuesto de la presente invención se puede emplear en conjunción con agentes anti-eméticos para tratar náuseas o émesis, incluyendo émesis aguda, retardada, de fase tardía, y anticipatoria, la cual puede resultar del uso de un compuesto de la presente invención, solo o con terapia

de radiación. Para la prevención o tratamiento de émesis, un compuesto de la presente invención se pueden usar en conjunción con otros agentes antieméticos, especialmente antagonistas de receptor de neuroquinina-1, antagonistas de receptor de 5HT3, tal como ondansetrón, granisetrón, tropisetrón, y zatisetrón, agonistas de receptor de GABAB, tales como baclofeno, un corticosteroide tal como Decadrón (dexametasona), Kenalog, Aristocort, Nasalida, Preferid, Benecorten u otros tales como se describe en las Patentes de los Estados Unidos N$^{os}$.: 2.789.118, 2.990.401, 3.048.581, 3.126.375, 3.929.768, 3.996.359, 3.928.326 y 3.749.712, un antidopaminérgico, tales como las fenotiazinas (por ejemplo proclorperazina, flufenazina, tioridazina y mesoridazine), metoclopramida o dronabinol. En otra realización, se describe la terapia conjuntiva con un agente antiémesis seleccionado de un antagonista de receptores de neuroquinina-1, un antagonista de receptores de 5HT3 y un corticosteroide para el tratamiento o prevención de émesis que puede resultar de administración de los compuestos actuales.

Antagonistas de receptor de neuroquinina-1 de uso en conjunción con los compuestos de la presente invención se describen totalmente, por ejemplo, en las Patentes de los Estados Unidos N$^{os}$.: 5.162.339, 5.232.929, 5.242.930, 5.373.003, 5.387.595, 5.459.270, 5.494.926, 5.496.833, 5.637.699, 5.719.147; Publicación de Patentes Europeas N$^{os}$.: EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 y 0 776 893; Publicación de Patentes Internacionales PCT N$^{os}$.: WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 y 97/21702; y en Publicación de Patentes Británicas N$^{os}$.: 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, y 2 302 689. La preparación de tales compuestos se describe planamente en las patentes y publicaciones mencionadas, las cuales están incorporadas en el presente documento mediante referencia.

En una realización, el antagonista de receptor de neuroquinina-1 para usar en conjunción con los compuestos de la presente invención se selecciona de: 2-(R)-(1-(R)-(3,5-

bis(trifluorometil)fenil)etoxi)-3-(S)-(4-fluorofenil)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)metil)morfolina, o una sal farmacéuticamente aceptable de la misma, la cual se describe en la Patente de los EE.UU. 5.719.147.

Un compuesto de la invención actual se puede administrar también con un agente útil en el tratamiento de anemia. Un tratamiento de anemia tal es, por ejemplo, un activador de receptor de eritropoyesis continua (tal como epoetina alfa).

Un compuesto de la invención actual se puede administrar también con un agente útil en el tratamiento de neutropenia. Un agente tal de tratamiento de neutropenia es, por ejemplo, un factor de crecimiento hematopoyético el cual regula la producción y función de neutrófilos tales como un factor estimulador de colonias de granulocitos humanas, (G-CSF). Ejemplos de un G-CSF incluyen filgrastim.

Un compuesto de la invención actual se puede administrar también con un fármaco de potenciación inmunológica, tal como levamisol, isoprinosina y Zadaxin.

Un compuesto de la invención actual puede ser también útil para tratar o prevenir cáncer en combinación con inhibidores de P450 que incluyen: xenobióticos, quinidina, tiramina, ketoconazol, testosterona, quinina, metirapona, cafeína, fenelzina, doxorrubicina, troleandomicina, ciclobenzaprina, eritromicina, cocaína, furafilina, cimetidina, dextrometorfano, ritonavir, indinavir, amprenavir, diltiazem, terfenadina, verapamil, cortisol, itraconazol, mibefradilo, nefazodona y nelfinavir.

Un compuesto de la invención actual puede ser también útil para tratar o prevenir cáncer en combinación con inhibidores de Pgp y/o de BCRP que incluyen: ciclosporina A, PSC833, GF120918, cremophorEL, fumitremorgina C, Ko132, Ko134, Iressa, mesilato de imatnib, EKI-785, CI1033, novobiocina, dietilestilbestrol, tamoxifeno, resperpina, VX-710, triprostatina A, flavonoides, ritonavir, saquinavir, nelfinavir, omeprazol, quinidina, verapamilo, terfenadina, ketoconazol, nifidepina, FK506, amiodarona, XR9576, indinavir, amprenavir, cortisol, testosterona, LY335979, OC144-093, eritromicina, vincristina, digoxina y talinolol.

Un compuesto de la invención actual puede ser también útil para tratar o prevenir cancer, incluyendo cáncer de huesos, en combinación con bisfosfonatos (entendidos para incluir bisfosfonatos, difosfonatos, ácidos bisfosfónicos y ácidos difosfónicos). Ejemplos de bisfosfonatos incluyen pero no se limitan a: etidronato (Didronel), pamidronato (Aredia), alendronato (Fosamax), risedronato (Actonel), zoledronato (Zometa), ibandronato (Boniva), incadronato o cimadronato, clodronato, EB-1053, minodronato, neridronato, piridronato y tiludronato que incluyen cualquiera y todas las sales farmacéuticamente aceptables, derivados, hidratos y mezclas de los mismos.

Un compuesto de la invención actual puede también ser útil para tratar o prevenir cáncer de mama en combinación con inhibidores de aromatasa. Ejemplos de inhibidores de aromatasa incluyen pero no se limitan a: anastrozol, letrozol y exemestano.

Un compuesto de la invención actual puede también ser útil para tratar o prevenir cáncer en combinación con compuestos terapéuticos de RNAip.

Los compuestos de la invención actual se pueden administrar también en combinación con inhibidores de γ-secretasa y/o inhibidores de señalización NOTCH. Tales inhibidores incluyen compuestos descritos en documentos WO 01/90084, WO 02/30912, WO 01/70677, WO 03/013506, WO 02/36555, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 2004/039800, WO 2004/039370, WO 2005/030731, WO 2005/014553, USSN 10/957.251, WO 2004/089911, WO 02/081435, WO 02/081433, WO 03/018543, WO 2004/031137, WO 2004/031139, WO 2004/031138, WO 2004/101538, WO 2004/101539 y WO 02/47671 (incluyendo LY-450139).

Inhibidores de Akt, como se describen en las siguientes publicaciones; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, y que incluyen compuestos de la invención actual son también útiles en combinación con sales de potasio, sales de magnesio, beta-bloqueantes (tales como atenolol) y antagonistas de endotelina-a (ETa) con la meta de mantener homeostasis cardiovascular.

Inhibidores de Akt, como se describen en las siguientes publicaciones; WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344, US 2005/029941, US 2005/44294, US 2005/43361, 60/734188, 60/652737, 60/670469, y que incluyen compuestos de la invención actual son también útiles en combinación con insulina, secretagogos de insulina, agonistas de PPAR-gamma, metformina, agonistas de receptor de somatostatina tales como octreotida, inhibidores de DPP4, sulfonilureas e inhibidores de alfa-glucoxidasa con la meta de mantener homeostasis de glucosa.

Un compuesto de la invención actual puede también ser útil para tratar o prevenir cáncer en combinación con inhibidores de PARP.

Un compuesto de la invención actual puede ser también útil para tratar cáncer en combinación con los siguientes agentes terapéuticos: abarelix (Plenaxis depot®); aldesleucina (Prokine®); Aldesleucina (Proleukin®); Alemtuzumabb (Campath®); alitretinoína (Panretin®); alopurinol (Zyloprim®); altretamina (Hexalen®); amifostina (Ethyol®); anastrozol (Arimidex®); trióxido de arsénico (Trisenox®); asparraginasa (Elspar®); azacitidina (Vidaza®); bevacuzimab (Avastin®); cápsulas de bexaroteno (Targretin®); gel de bexaroteno (Targretin®); bleomicina (Blenoxane®); bortezomib (Velcade®); busulfán intravenoso (Busulfex®); busulfán oral (Myleran®); calusterona (Methosarb®); capecitabina (Xeloda®); carboplatina (Paraplatin®); carmustina (BCNU®, BiCNU®); carmustina (Gliadel®); carmustina con Implante de Polifeprosan 20 (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); clorambucilo (Leukeran®); cisplatina (Platinol®);

cladribina (Leustatin®, 2-CdA®); clofarabina (Clolar®); ciclofosfamida (Cytoxan®, Neosar®); ciclofosfamida (Cytoxan Injection®); ciclofosfamida (Cytoxan Tablet®); citarabina (Cytosar-U®); citarabina liposomal (DepoCyt®); dacarbazina (DTIC-Dome®); dactinomicina, actinomicina D (Cosmegen®); darbepoetina alfa (Aranesp®); daunorrubicina liposomal (DanuoXome®); daunorrubicina, daunomicina (Daunorubicin®); daunorrubicina, daunomicina (Cerubidine®); Denileucina diftitox (Ontak®); dexrazoxano (Zinecard®); docetaxel (Taxotere®); doxorrubicina (Adriamycin PFS®); doxorrubicina (Adriamycin®, Rubex®); doxorrubicina (Adriamycin PFS Injection®); doxorrubicina liposomal (Doxil®); propionato de dromostanolona (dromostanolone®); propionato de dromostanolona (masterone injection®); Solución B de Elliott (Elliott's B Solution®); epirrubicina (Ellence®); Epoetina alfa (epogen®); erlotinib (Tarceva®); estramustina (Emcyt®); fosfato de etopósido (Etopophos®); etopósido, VP-16 (Vepesid®); exemestano (Aromasin®); Filgrastim (Neupogen®); floxuridina (intraarterial) (FUDR®); fludarabina (Fludara®); fluorouracilo, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabina (Gemzar®); ozogamicina de gemtuzumab (Mylotarg®); acetato de goserelina (Zoladex Implant®); acetato de goserelina (Zoladex®); acetato de histrelina (Histrelin implant®); hidroxiurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarrubicina (Idamycin®); ifosfamida (IFEX®); mesilato de imatinib (Gleevec®); interferón alfa 2a (Roferon A®); interferón alfa-2b (Intron A®); irinotecán (Camptosar®); lenalidomida (Revlimid®); letrozol (Femara®); leucovorina (Wellcovorin®, Leucovorin®); Acetato de Leuprolida (Eligard®); levamisol (Ergamisol®); lomustina, CCNU (CeeBU®); mecloretamina, mostaza de nitrógeno (Mustargen®); acetato de megestrol (Megace®); melfalán, L-PAM (Alkeran®); mercaptopurina, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); metotrexato (Methotrexate®); metoxaleno (Uvadex®); mitomicina C (Mutamycin®); mitotano (Lysodren®); mitoxantrona (Novantrone®); fenpropionato de nandrolona (Durabolin-50®); nelarabina (Arranon®); Nofetumomab (Verluma®); Oprelvekina (Neumega®); oxaliplatina (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); partículas de paclitaxel unidas a proteínas (Abraxane®); palifermina (Kepivance®); pamidronato (Aredia®); pegademasa (Adagen (Pegademase Bovine)®); pegaspargasa (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disódico (Alimta®); pentostatina (Nipent®); pipobroman (Vercyte®); plicamicina, mitramicina (Mithracin®); porfimer sodio (Photofrin®); procarbazina (Matulane®); quinacrina (Atabrine®); Rasburicasa (Elitek®); Rituximab (Rituxan®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); estreptozocina (Zanosar®); maleato de sunitinib (Sutent®); talco (Sclerosol®); tamoxifeno (Nolvadex®); temozolomida (Temodar®); tenipósido, VM-26 (Vumon®); testolactona (Teslac®); tioguanina, 6-TG (Thioguanine®); tiotepa (Thioplex®); topotecán (Hycamtin®); toremifeno (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretinoína, ATRA (Vesanoid®); Mostaza de Uracilo (Uracil Mustard Capsules®); valrubicina (Valstar®); vinblastina (Velban®); vincristina (Oncovin®); vinorrelbina (Navelbine®); y zoledronato (Zometa®).

Así, el alcance de la invención actual comprende el uso de los compuestos actualmente reivindicados en combinación con un segundo compuesto seleccionado de: un modulador de receptor de estrógenos, un modulador de receptor de andrógenos, un modulador de receptor de retinoides, un agente citotóxico/citostático, un agente antiproliferativo, un inhibidor de prenil-proteintransferasa, un inhibidor de HMG-CoA reductasa, un inhibidor de proteasa de VIH, un inhibidor de transcriptasa reversa, un inhibidor de angiogénesis, agonistas de PPAR-γ, agonistas de PPAR-δ, un inhibidor de resistencia a multifármacos inherente, un agente antiemético, un agente útil en el tratamiento de anemia, un agente útil en el tratamiento de neutropenia, un fármaco de potenciación inmunológica, un inhibidor de proliferación celular y señalización de supervivencia, un bisfosfonato, un inhibidor de aromatasa, un RNAip terapéutico, inhibidores de γ-secretasa, agentes que interfieren con tirosina quinasas receptoras (RTK), un agente que interfiere con un punto de control del ciclo celular y cualquiera de los agentes terapéuticos enumerados anteriormente.

El término "administración" y variantes del mismo (por ejemplo, "administrar" un compuesto) en referencia a un compuesto de la invención significa introducir el compuesto o un porfármaco del compuesto dentro del sistema del animal en necesidad de tratamiento. Cuando un compuesto de la invención o profármaco del mismo se proporciona en combinación con uno o más agentes activos diferentes (por ejemplo, un agente citotóxico, etc.), "administración" y sus variantes se entienden de forma que cada una incluye introducción concurrente y secuencial del compuesto o profármaco del mismo y otros agentes.

Tal como se usa en la presente memoria el término "composición" se pretende que englobe un producto que comprende los ingredientes especificados en las cantidades especificadas, así como cualquier producto que resulte de forma directa o indirecta de la combinación de los ingredientes especificados en las cantidades especificadas.

El término "cantidad terapéuticamente efectiva" como se usa en el presente documento significa aquella cantidad de compuesto activo o agente farmacéutico que facilita la respuesta biológica o médica en un tejido, sistema, animal o ser humano, que se intenta conseguir por un investigador, veterinario, doctor médico u otro trabajador clínico.

El término "tratar cáncer" o "tratamiento de cáncer" hace referencia a administración a un mamífero afligido con una afección cancerosa y se refiere a un efecto que alivia la afección cancerosa matando las células cancerosas, pero también a un efecto que da como resultado la inhibición de crecimiento y/o metástasis del cáncer.

En una realización, el inhibidor de angiogénesis para usarse como el segundo compuesto se selecciona de un inhibidor de tirosina quinasa, un inhibidor de factor de crecimiento derivado de la epidermis, un inhibidor de factor de crecimiento derivado de fibroblastos, un inhibidor de factor de crecimiento derivado de plaquetas, un inhibidor de MMP (metaloproteasa de matriz), un bloqueante de integrinas, interferon-α, interleucina-12, polisulfato de pentosano, un inhibidor de ciclooxigenasa, carboxiamidotriazol, combretastatina A-4, esqualamina, 6-O-cloroacetil-carbonil)-fumagilol, talidomida,

angiostatina, troponina-1, o un anticuerpo contra VEGF. En una realización, el modulador de receptor de estrógenos es tamoxifeno o raloxifeno.

También está incluido en el alcance de las reivindicaciones un procedimiento de tratar cáncer que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la invención actual en combinación con terapia de radiación y/o en combinación con un segundo compuesto seleccionado de: un modulador de receptores de estrógenos, un modulador de receptores de andrógenos, un modulador de receptores retinoides, un agente citoóxico-citostático, un agente antiproliferativo, un inhibidor de prenil-proteintransferasa, un inhibidor de HMG-CoA reductasa, un inhibidor de proteasa de VIH, un inhibidor de transcriptasa reversa, un inhibidor de angiogénesis, agonistas de PPAR-γ, agonistas de PPAR-δ, un inhibidor de resistencia a multifármacos inherente, un agente antiemético, un agente útil en el tratamiento de anemia, un agente útil en el tratamiento de neutropenia, un fármaco potenciador inmunológico, un inhibidor de proliferación y de señalización de supervivencia, un bisfosfonato, un inhibidor de aromatasa, un RNAip terapéutico, inhibidores de γ-secretasa, agentes que interfieren con tirosina quinasas de receptor (RTK), un agente que interfiere con un punto de control del ciclo celular y cualquiera de los agentes terapéuticos enumerados anteriormente.

Y aún otra realización de la invención es un procedimiento para tratar cáncer que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la invención actual en combinación con paclitaxel o trastuzumab.

La invención comprende adicionalmente un procedimiento de tratar o prevenir cáncer que comprende administrar una cantidad terapéuticamente efectiva de un compuesto de la invención actual en combinación con un inhibidor de COX-2.

La invención actual también incluye una composición farmacéutica útil para tratar o prevenir cáncer que comprende una cantidad terapéuticamente efectiva de un compuesto de la invención actual y un segundo compuesto seleccionado de: un modulador de receptores de estrógenos, un modulador de receptores de andrógenos, un modulador de receptores retinoides, un agente citotóxico/citostático, un agente antiproliferativo, un inhibidor de prenil-proteintransferasa, un inhibidor de HMG-CoA reductasa, un inhibidor de proteasa de VIH, un inhibidor de transcriptasa reversa, un inhibidor de angiogénesis, agonistas de PPAR-γ, agonistas de PPAR-δ, un inhibidor de proliferación celular y señalización de supervivencia, un bisfosfonato, un inhibidor de aromatasa, un RNAip terapéutico, inhibidores de γ-secretasa, agentes que interfieren con tirosina quinasas receptoras (RTK), un agente que interfiere con un punto de control del ciclo celular y cualquiera de los agentes terapéuticos enumerados anteriormente.

Todas las patentes, publicaciones y solicitudes de patente pendientes identificadas están incorporadas en el presente documento mediante referencia.

Las abreviaturas usadas en la descripción de la química y en los Ejemplos que siguen son: AEBSF (fluoruro de p-aminoetilbencenosulfinilo); BSA (seroalbúmina bovina); BuLi (n-butillitio); $CDCl_3$ (cloroformo-d); CuI (yoduro de cobre); $CuSO_4$ (sulfato de cobre); DCE (dicloroetano); DCM

(diclorometano); DEAD (dietilazodicarboxilato); DMF (N,N-dimetilformamida); DMSO (dimetilsulfóxido); DTT (ditiotreitol); EDTA (ácido etileno-diamina-tetra-acético); EGTA (ácido etileno-glicol-tetra-acético); EtOAc (acetato de etilo); EtOH (etanol); HOAc (ácido acético); HPLC (cromatografía líquida de alta resolución); HRMS (espectro de masas de alta resolución); CLEM (cromatógrafo líquido-espectrómetro de masas); LHMDS (bis(trimetilsilil)amida de litio); LREM (espectro de masas de baja resolución); MeOH (metanol); MP-B(CN)$H_3$ (cianoborohidruro macroporoso); $NaHCO_3$ (bicarbonato de sodio); $Na_2SO_4$ (sulfato de sodio); $Na(OAc)_3BH$ (triacetoxiborohidruro de sodio); $NH_4OAc$ (acetato de amonio); NBS (N-bromosuccinamida); RMN (resonancia magnética nuclear); PBS (solución salina tamponada con fosfato); PCR (reacción en cadena de la polimerasa); Pd(dppf) ([1,1'-bis(difenilfosfino)ferroceno] paladio); $Pd(Ph_3)_4$ (tetrakis-trifenilfosfina de paladio(0)); $POCl_3$ (oxicloruro de fósforo); PS-DIEA (diisopropiletilamina de poliestireno); PS-$PPh_3$ (poliestireno-trifenilfosfina); TBAF (fluoruro de tetrabutilamonio); THF (tetrahidrofurano); TFA (ácido trifluoroacético); $TMSCH_2N_2$ (trimetilsilildiazometano) y Ac (acetilo); BOC (t-butoxicarbonilo); Bu (butilo); Cal (calculado); Calc. (calculado); DIEA (diisopropiletilamina); DMAP (4-dimetilaminopiridina); EDC (N-etil-N'-(3-dimetilaminopropil)carbodiimida); Eq (equivalentes); Et (etilo); HOBT (hidroxibenzotriazol); IPA (isopropanol); CL/EM (cromatógrafo líquido-espectrometría de masas); Me (metilo); MeCN (acetonitrilo); NMP (N-metilpirrolidinona); Pr (propilo); Pir (piridina); Sat (saturado) y Tósico (ácido p-toluenosulfónico).

Los compuestos de esta invención se pueden preparar empleando reacciones como se muestra en el siguiente Esquema de Reacciones, además de otras manipulaciones estándar que se conocen en la bibliografía o se ejemplifican en los procedimientos experimentales. El Esquema de Reacciones ilustrativo más adelante, no está limitado por los compuestos enumerados o por cualesquiera sustituyentes particulares empleados para propósitos ilustrativos. La numeración sustituyente como se muestra en el Esquema de Reacciones no correlaciona necesariamernte con aquella usada en las reivindicaciones y a menudo, para claridad, se muestra un único sustituyente anclado al compuesto donde múltiples sustituyentes están permitidos bajo las definiciones de Fórmula A anteriormente en el presente documento.

La síntesis inicial de los compuestos actuales se muestra en los Esquemas de Reacción I-IX. Las reacciones finales que se pueden usar para generar los compuestos de esta invención se muestran en los Esquemas de Reacción X-XIV.

Sinopsis de Esquemas de Reacción

Los siguientes Esquemas de Reacción, Esquemas de Reacción I-IX, proporcionan detalles útiles para preparar los restos bicíclicos de los compuestos actuales.

Los intermedios requeridos están en algunos casos comercialmente disponibles, o se pueden preparar de acuerdo con procedimientos en la bibliografía. Como se ilustra en el Esquema de Reacción I, una fenilacetilida adecuadamente sustituida se puede hacer reaccionar con yoduro de cobre para formar la correspondiente acetilida de cobre **I-1** (véase por ejemplo, Sonogashira, K.; Toda, Y.;

Hagihara, N. *Tetrahedron Lett.* 1975, 4467). Se puede hacer reaccionar el intermedio **I-1** con un resto electrofílico adecuadamente sustituido para proporcionar el **I-2** asimétricamente sustituido. La reacción con NBS seguida por hidrólisis proporciona **I-3** (véase por ejemplo, Yusybov, M.S.; Filimonov, V.D.; *Synthesis* 1991, *2*, 131). Una diversidad de arilos y heterociclilos sustituidos puede también obtenerse comercialmente.

El Esquema de Reacción II ilustra la preparación de los compuestos, comenzando con un **II-1** adecuadamente sustituido. Este intermedio puede hacerse reaccionar con una amina adecuadamente sustituida para proporcionar intermedio **II-2**, el cual puede hacerse reaccionar con una aril o heteroarildiamina adecuada para proporcionar una mezcla regioisómera de los compuestos actuales, los cuales usualmente se pueden separar cromatográficamente.

El Esquema de Reacción III ilustra la síntesis de otro heterociclilo bicíclico.

El Esquema de Reacción IV ilustra la preparación de los compuestos, comenzando con un 4-amino-3-nitrobenzonitrilo **IV-I** adecuadamente sustituido. Este intermedio se puede someter a una reacción de cicloadición [3+2] promovida por microondas para proporcionar tetrazol **IV-II**. La alquilación del tetrazol acídico con un electrófilo, tal como yoduro de metilo, administra una mezcla de 2-metilo(IV-III)/1-metilo(IV-IV) de tetrazoles alquilados los cuales son separables mediante cromatografía en columna. La hidrogenación Ra-Ni de **IV-III** administra la diamina **IV-V**. La síntesis adicional es como se describe en los Esquemas de Reacción anteriores.

El Esquema de Reacción V es ilustrativo para la síntesis de compuestos. La ciclocondensación de Friedlander de un arilo o aminoaldehído de heteroarilo con una cetona adecuadamente sustituida da intermedios de fórmula **V-1**. La conversión de la funcionalidad de ácido carboxílico a una funcionalidad de aldehído da intermedio **V-2** y se acompleja mediante procedimientos bien conocidos por aquellos expertos en la técnica. La alquilación reductiva con una amina adecuadamente sustituida proporciona compuestos de fórmula **V-3**.

El Esquema de Reacción VI ilustra una síntesis alternativa de intermedio **V-2**.

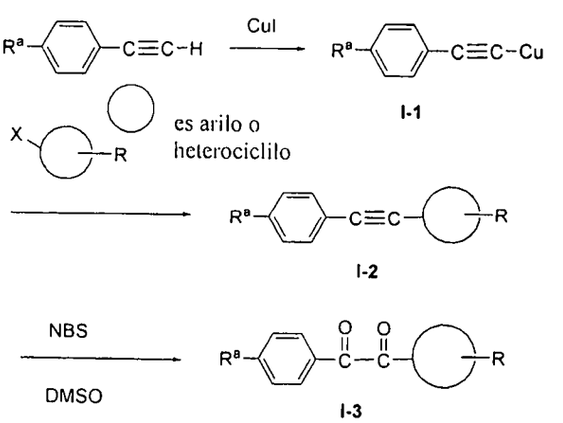
El Esquema de Reacción VII ilustra la síntesis de los compuestos, comenzando con cetona **VII-1** la cual se prepara de acuerdo con la bibliografía (Renault, O.; Dallemagne, P.; y Rault, S. *Org. Prep. Proced. Int.*, 1999, *31*, 324). La condensación de **VII-1** con N,N-dimetilformamida dimetilacética da ceto-enamina **VII-2**, la cual se hace cíclica con 2-cianoacetamida para proporcionar piridona **VII-3**. El tratamiento de **VII-3** con oxicloruro de fósforo produce cloropiridina **VII-4**. La bromination radical seguida por desplazamiento con aminas adecuadamente sustituidas genera aminas **VII-5**. La reacción subsiguiente de cloronicotinonitrilos **VII-5** con diversos bisnucleofilos proporciona las estructuras cicladas **VII-6**.

El Esquema de Reacción VIII ilustra la preparación de los compuestos de 1,6-naftiridin-6(5H)-ona. La síntesis comienza con un ácido carboxílico comercialmente disponible (**VIII-1**), el cual se convierte en amida Weinreb (**VIII-2**). La reacción de amida con un reactivo de arillitio, generada a través de reacción de intercambio litio-halógeno de un bromuro de arilo con n-butillitio, proporciona la cetona

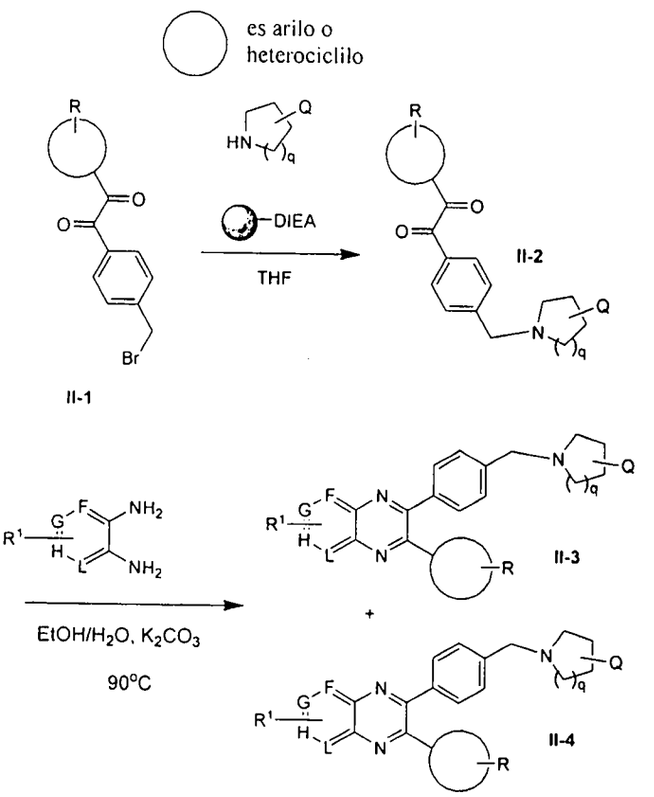
(**VIII-3**). La condensación de esta cetona sustituida con 4-aminonicotinaldehído en presencia de una base, por ejemplo, hidróxido de sodio o metóxido de sodio, da la 1,6-naftiridina (**VIII-4**). El sustituyente R en el fenilo puede ser un grupo funcional, tal como, un hidroximetilo (silil)protegido, el aldehído enmascarado (es decir acetal), o un ácido carboxílico. Este material se puede convertir al aldehído requerido **VIII-4**. Cuando el grupo R es hidroximetilo, la oxidación con un reactivo tal como dióxido de manganeso activado da el aldehído **VIII-4**. Cuando R es un acetal, la hidrólisis de ácidos débiles da el aldehído. La reducción del grupo ácido carboxílico por medio de reducción de un anhídrido mezclado con un borohidruro da también el aldehído **VIII-4**. Este aldehído puede sufrir después aminación reductora con una disposición diversa de aminas, por ejemplo, una piperidina 4-sustituida, y un borohidruro para proporcionar 1,6-naftiridin-5(H)-onas (**VIII-5**). El tratamiento de (**VIII-5**) con clorhidrato de piridinio a 150°C suministra el producto final (**VIII-6**).

El Esquema de Reacción IX ilustra una estrategia alternativa de introducir heterociclos en la posición C3. Ello comienza con diclorobenzopirazona comercialmente disponible, la cual puede acoplarse a un ácido arilbórico en presencia de un catalizador de paladio (reacción de Suzuki). Después una repetición de esta reacción con otro ácido bórico heteroclíco proporciona el producto final, bajo las mismas condiciones de reacción.

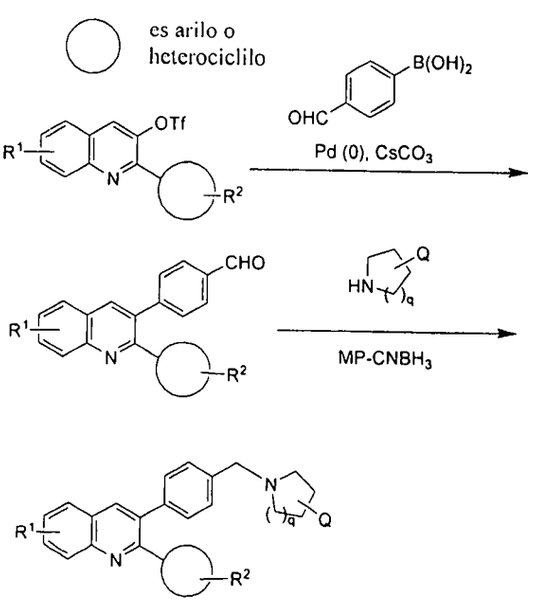
Esquema de Reacción I



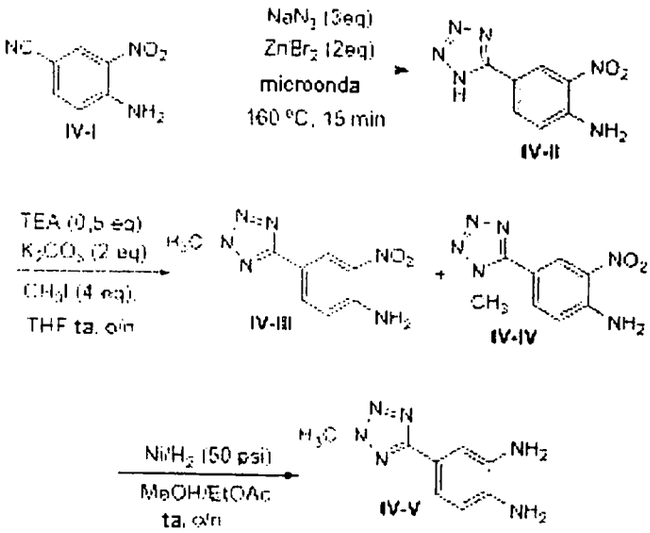
Esquema de Reacción II



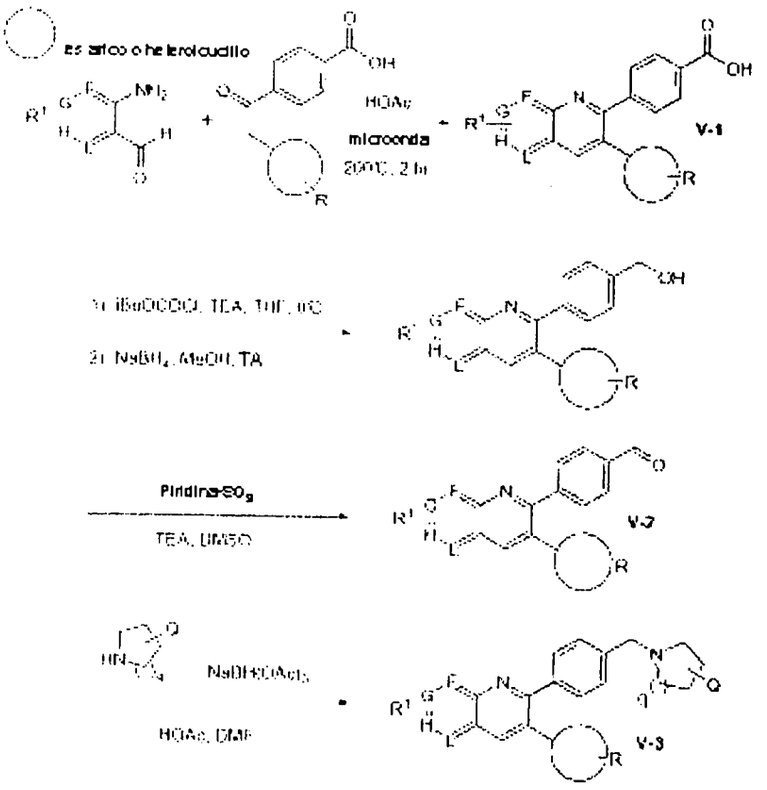

Esquema de Reacción III



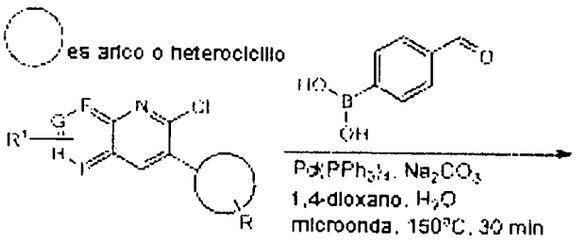
Esquema de Reacción IV

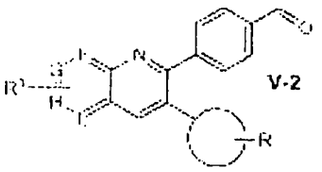



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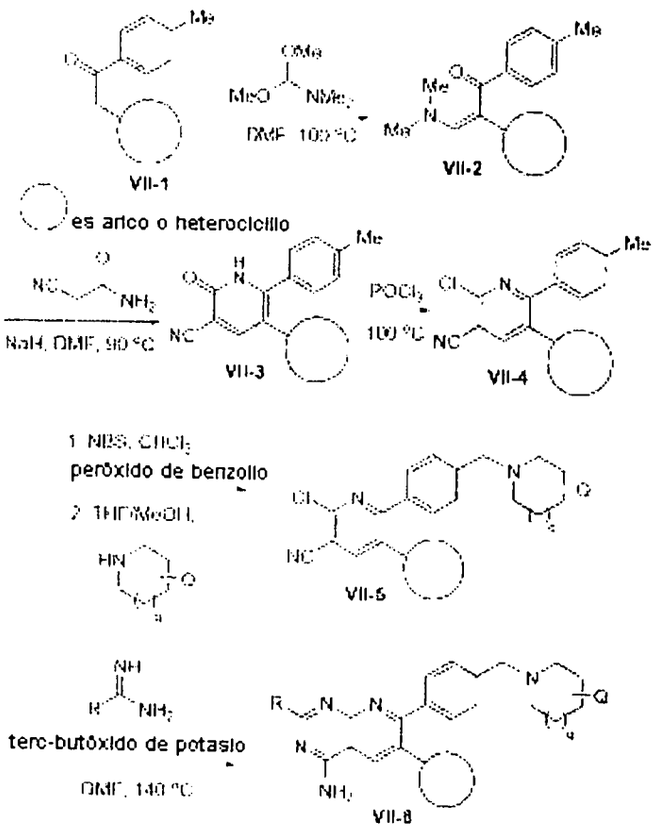
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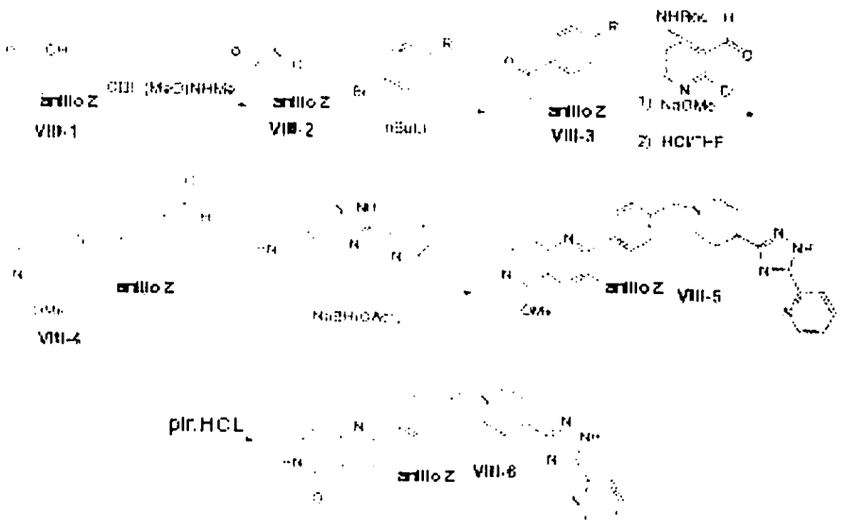



V-2

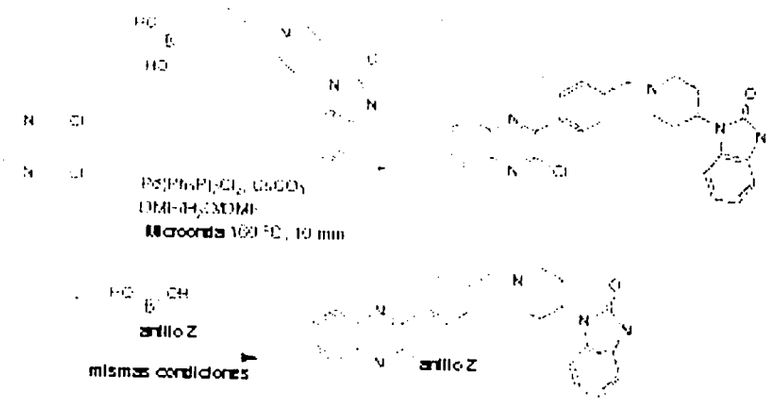
Esquema de Reacción VII



Esquema de Reacción VIII




Esquema de Reacción IX




Sinopsis Final de Esquemas de Reacción

Los siguientes Esquemas de Reacción, Esquemas de Reacción X-XIV, proporcionan detalles útiles para preparar los restos tricíclicos de los compuestos actuales.

Los intermedios requeridos están en algunos casos comercialmente disponibles, o se pueden preparar de acuerdo con procedimientos en la bibliografía. El tratamiento de un intermedio arilo o heteroarilo adecuadamente sustituido **X-1** con $POCl_3$ da intermedios de fórmula **X-2**. La conversión de la funcionalidad de cloruro a una funcionalidad de hidrazida da intermedio **X-3** y se lleva a cabo

mediante procedimientos bien conocidos por aquellos expertos en la técnica. La ciclización con un precursor de diimidazol adecuado proporciona compuestos de fórmula **X-4**.

El Esquema de Reacción XI ilustra una síntesis alternativa de compuestos de fórmula **X-4**.

El Esquema de Reacción XII ilustra síntesis de compuestos de fórmula **XII-2**. La condensación de **X-3** con trimetoxicloroacetato apropiado da intermedio de clorometilo **XII-1**, el cual, por medio de un desplazamiento nucleofílico, proporciona estructura **XII-2**.

El Esquema de Reacción XIII ilustra la preparación de los compuestos de triazolonaftiridina. La síntesis comienza con naftiridona conocida de bibliografía/patentes (**XIII-1**), la cual se convierte a cloruro de naftiridina (**XIII-2**) después del tratamiento de $POCl_3$ bajo condiciones de reflujo. La reacción del último compuesto con hidrazina pura, y bajo condición de reflujo, proporciona la hidrazida (**XIII-3**) la cual sirve como un intermedio clave para la síntesis de compuestos de triazolonaftiridina. La conversión de esta hidrazida (**XIII-4**) a los compuestos de triazolonaftiridina requeridos bajo las condiciones indicadas completan la síntesis planeada. El sustituyente R en el resto triazolo puede ser un grupo funcional, tal como, un grupo amino, un grupo oxo o un grupo tiol.

El Esquema de Reacción XIV ilustra una estrategia alternativa de introducir el resto triazolo en la parte a mano izquierda de la molécula. Comienza con intermedio hidrazida previamente sintetizado (**XIII-3**) el cual se puede tratar con un trimetoxiortoacetato para suministrar el producto final deseado, compuestos de tiazolonaftiridina (**XIV-1**). El sustituyente R en el resto triazolo puede ser un grupo funcional, tal como, un protón, un grupo alquilo simple, un grupo clorometilo o un grupo alquilo funcionalizado.

El Esquema de Reacción **XV** ilustra la síntesis de compuestos de fórmula **XV-1** usando tres procedimientos de aminación reductiva diferentes para introducir una amina primaria en la posición bencílica. Los procedimientos son también aplicables a otros aldehídos tales como compuestos de fórmula **XVII-1**.

El Esquema de Reacción **XVI** ilustra la síntesis de compuestos de fórmula **XVI-2** usando una variante de las condiciones para la ciclocondensación mostrada en el Esquema de Reacción **VIII**. El uso de un disolvente aprótico y una base da acceso a cloronaftiridinas de estructura **XVI-2**.

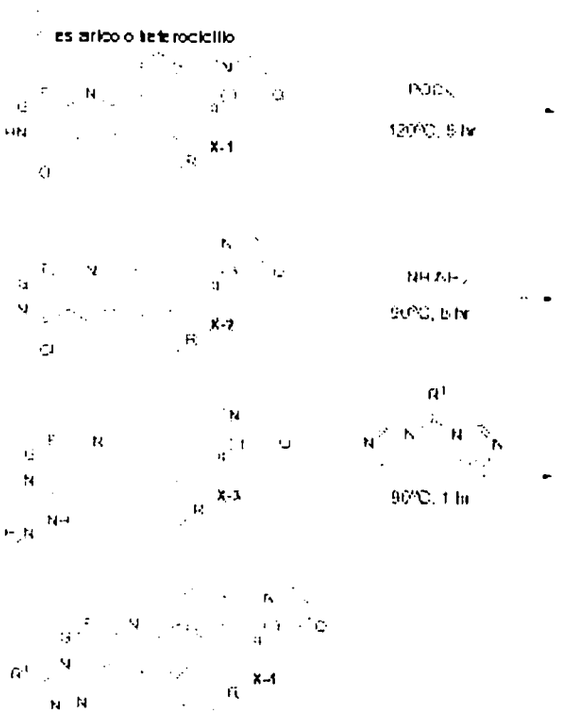
El Esquema de Reacción **XVII** ilustra la síntesis de compuestos de fórmula **XVII-4**. En este caso un sustituyente de metilo se introduce en la posición bencílica por medio de sulfinamida **XVII-2**. Otros sustituyentes se pueden introducir usando reactivos organometálicos tales como reactivos de Grignard. La t-butilsulfinimida se puede escindir usando un ácido tal como HCl para dar la amina.

El Esquema de Reacción **XVIII** ilustra la síntesis de compuestos de fórmula **XVIII-2** como una variante de la síntesis de triazol descrita en el Esquema de Reacción **XI**. En este caso la hidrazina **XVIII-1** se acopla a un ácido carboxílico y el intermedio acilhidrazina se cicla al triazol condensado bajo catálisis ácida.

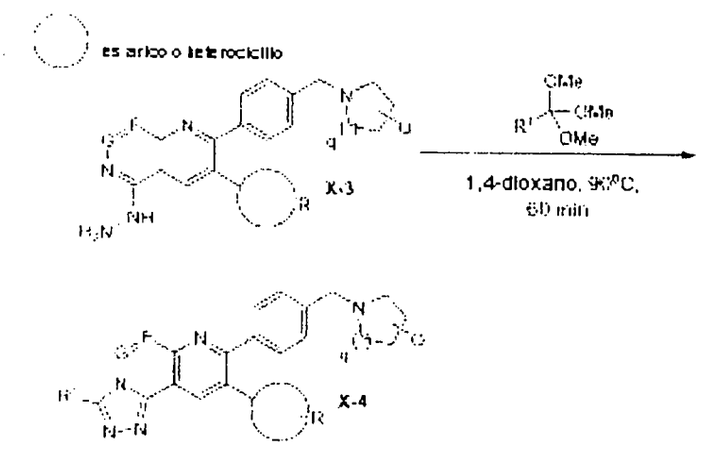
El Esquema de Reacción **XIX** ilustra la síntesis de compuestos de fórmula **XIX-2** en los cuales la ciclopropilamina se sintetiza a partir del nitrilo **XIX-1**.

El Esquema de Reacción **XX** ilustra la síntesis de compuestos de fórmula **XX-2** de aminas de fórmula **XX-1** bajo condiciones de aminación reductora estándar.

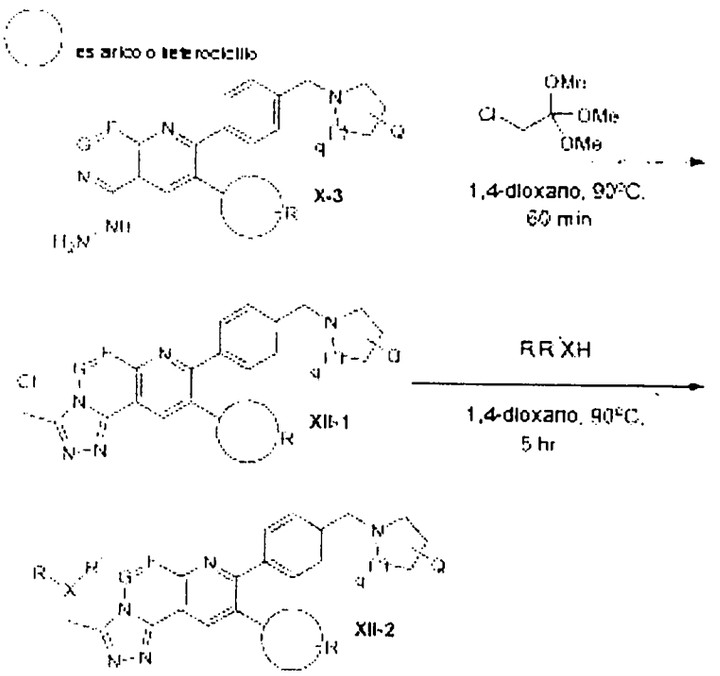
Esquema de Reacción X



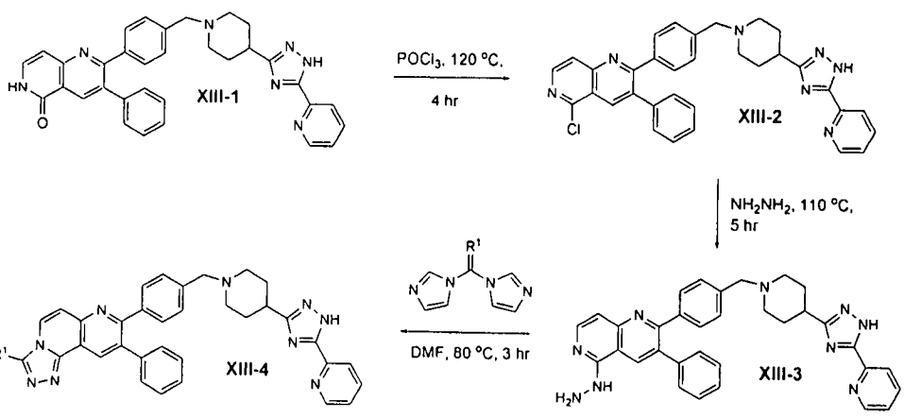

Esquema de Reacción XI



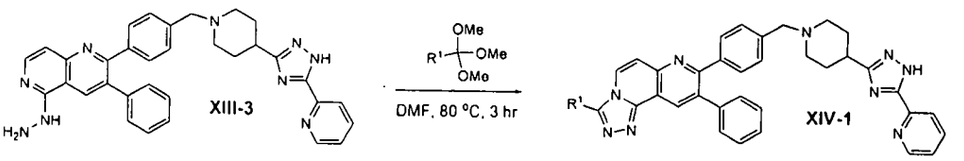
Esquema de Reacción XII



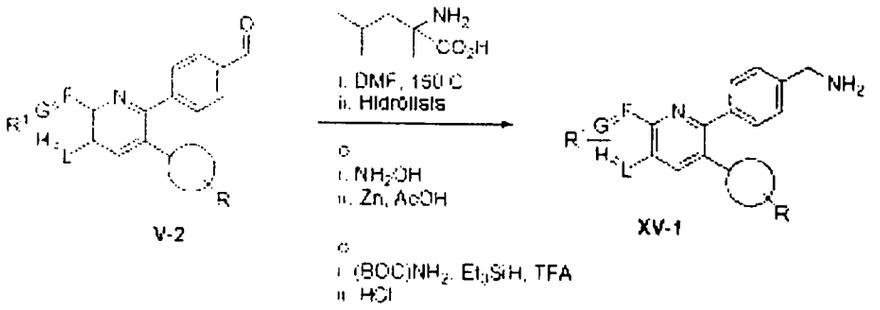

Esquema de Reacción XIII



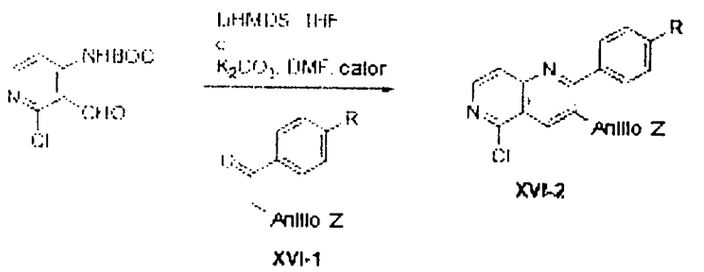

Esquema de Reacción XIV



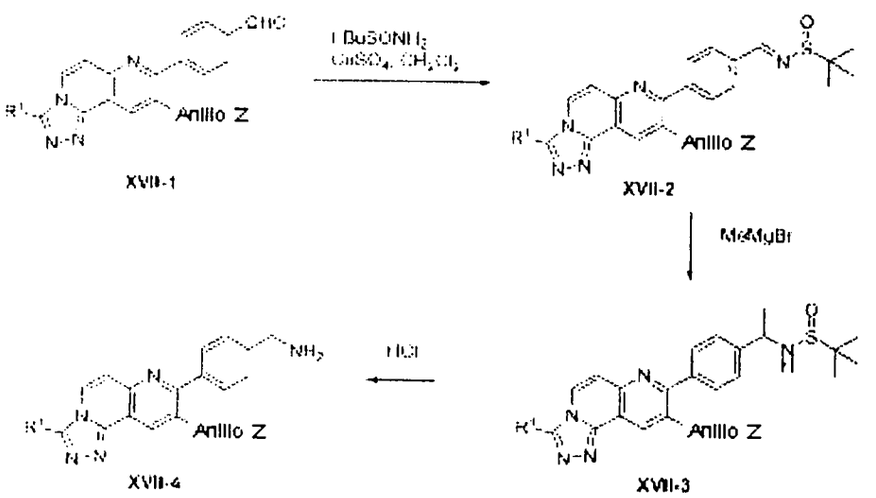

Esquema de Reacción XV



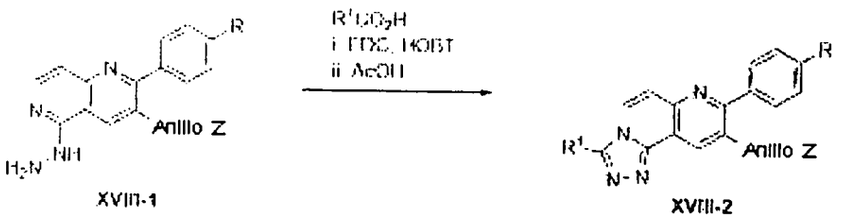

Esquema de Reacción XVI



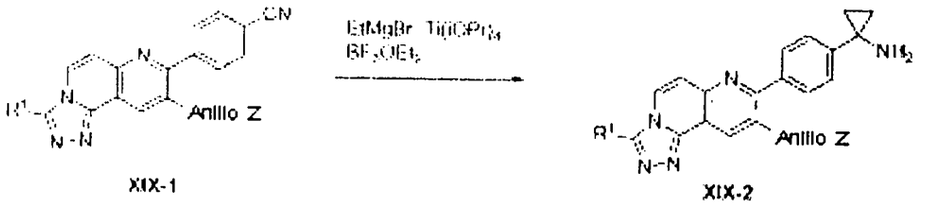

Esquema de Reacción XVII



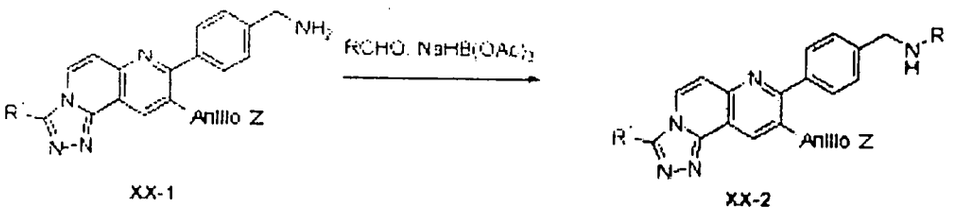
Esquema de Reacción XVIII




Esquema de Reacción XIX




Esquema de Reacción XX

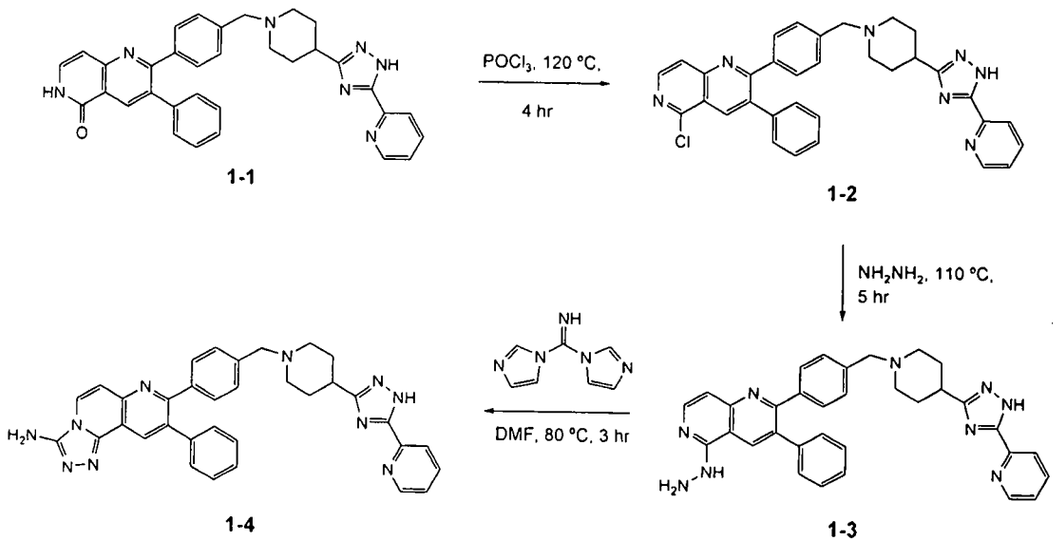



EJEMPLOS

Los ejemplos y esquemas proporcionados se desean para ayudar en una comprensión adicional de la invención. Los materiales particulares empleados, las especies y condiciones se desean para ser ilustrativas de la invención y no limitar el alcance razonable de la misma.

210

ESQUEMA 1




9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-4**)

5-cloro-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)-1,6-naftilridina (**1-2**)

Un matraz de 25 ml de RB con una barra agitadora se cargó con 3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazo-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridin-5(6H)-ona (0,86 g, 1,6 mmol), seguida por $POCl_3$ anhidro (8 ml). La mezcla se calentó a 120 °C y se agitó bajo reflujo durante 4 horas. Después la reacción se enfrió a temperatura ambiente, la mezcla de reacción se añadió cuidadosamente a una mezcla de solución acuosa de $NaHCO_3$ saturada fría (20 ml) y EtOAc (20 ml). El pH de la fase acuosa se mantuvo a alrededor de pH 8-9 durante todo el proceso de desactivación. La solución acuosa se extrajo adicionalmente con EtOAc (15 ml) y el residuo se lavó con MeOH (20 ml). Las fases orgánicas se combinaron y concentraron *a vacío* dando 5-cloro-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftilridina (**1-2**) (900 mg). El material orgánico se usó directamente en la etapa siguiente sin purificaciones adicionales.

5-hidrazino-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)-1,6-naftiridina (**1-3**)

Un matraz de 25 ml de RB con una barra agitadora se cargó con 5-cloro-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftilridina (**1-2**) (900 mg, 1,6 mmol), seguida por $NH_2NH_2$ anhidro (8 ml). La suspensión se calentó a 110 °C y se agitó bajo reflujo durante 5 horas. Después la reacción se enfrió a temperatura ambiente, la mezcla de reacción se concentró *a vacío*

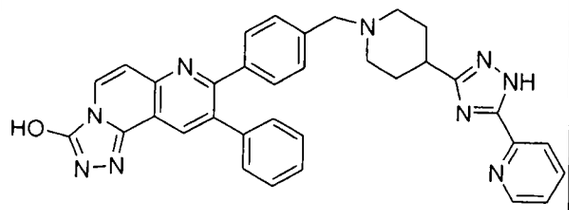
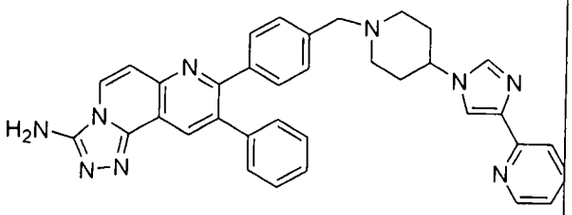
dando un polvo amarillento (900 mg). El producto en bruto se llevó a la siguiente etapa sin purificación adicional.

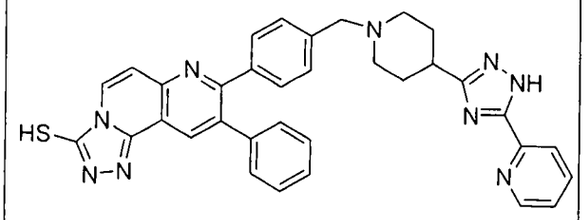
9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-4**)

A 5-hidrazino-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**1-3**) (70 mg, 0,126 mmol) en DMF (1,5 ml) se añadió 1,1-di-1H-imidazol-1-ilmetanimina conocida en la bibliografía (102 mg, 0,633 mmol). La mezcla de reacción se agitó a 85 °C durante 4 horas, se concentró *a vacío*, y se cromatografió suministrando la 9-fenil-8-(4-{[40(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil}[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**1-4**) deseada (46 mg) y su sal de ácido trifluoroacético. RMN $^1$H: (500 MHz, $CDCl_3$) δ 8,76 (s, 1H), 8,74 (d, *J*= 4,3 Hz, 1H), 8,29-8,27 (m, 2 H), 8,19 (m, 1H), 7,67 (m, 1H), 7,54-7,53 (m, 2H), 7,48-7,46 (m, 2H), 7,47 (d, *J*= 7,7 Hz , 1H), 7,34-7,26 (m, 5H), 4,43 (s, 2H), 3,65 (d a, *J*= 10,9 Hz, 2H), 3,46 (s a, 1 H), 3,27-3,19 (m, 2H), 2,50-2,42 (m, 2H), 2,10-2,06 (m, 2H).

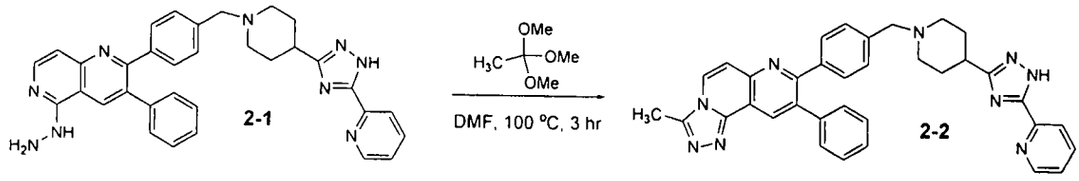
Los siguientes compuestos en la Tabla 1 se prepararon en una manera similar a como se muestra en el Esquema 1 y a como se muestra en los Esquemas de Reacción.

Tabla 1

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **1-5** |  | 9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-ol | 579,3 |
| **1-6** |  | 9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-amina | 577,3 |

| | | | |
|---|---|---|---|
| 1-7 |  | 9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-tiol | 595,2 |

ESQUEMA 2

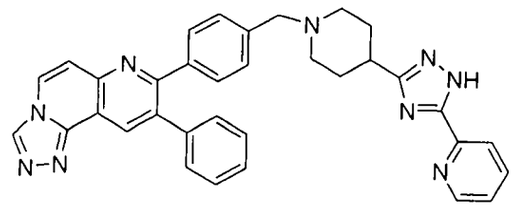


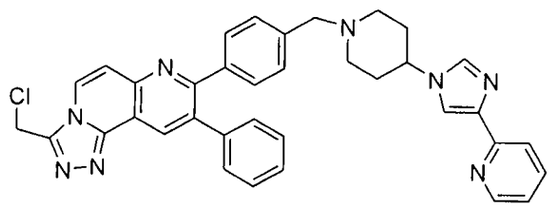
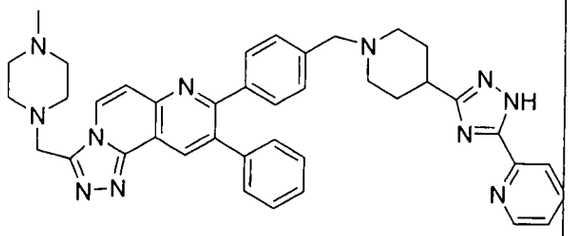
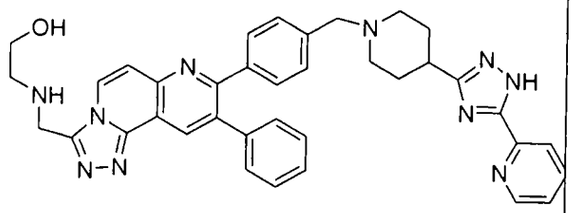

3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**2-2**)

A 5-hidrazino-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**2-1**) (55 mg, 0,101 mmol) en DMF (1,0 ml) se añadió ortoacetato de trimetilo (0,63 ml, 5,04 mmol). La mezcla de reacción se agitó a 100 °C durante 3 horas, y después se concentró *a vacío*, y se cromatografió suministrando la 3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina deseada (**2-2**) (28 mg) como su sal de ácido trifluoroacético. RMN $^1$H: (500 MHz, $CDCl_3$) δ 8,87 (s, 1H), 8,65 (d, *J*= 6,4 Hz, 1H), 8,33 (d, *J*= 7,5 Hz, 1H), 8,11 (d, *J*= 7,8 Hz, 1H), 7,92 (t, *J*= 7,8 Hz, 1H), 7,49-7,41 (m, 3 H), 7,36-7,30 (m, 8H), 3,61 (s, 2H), 3,02-3,00 (m, 2H), 3,00-2,84 (m, 1 H), 2,25-2,21 (m, 2H), 2,10-1,83 (m, 4H), 1,97 (s, 3H).

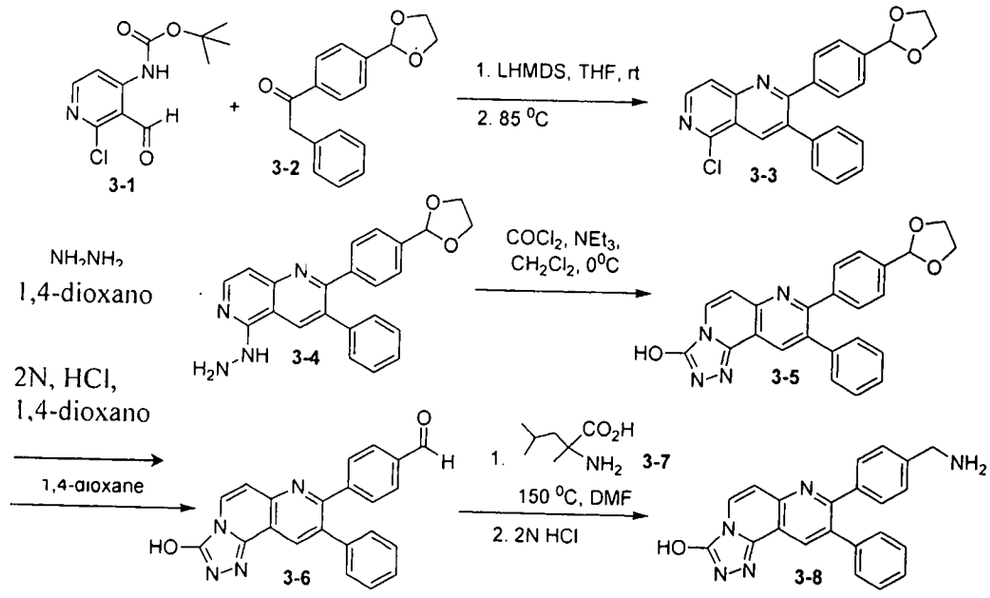
Los siguientes compuestos en la Tabla 2 se prepararon en una manera similar a como se muestra en el Esquema 2 y a como se muestra en los Esquemas de Reacción.

Tabla 2

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| 2-3 |  | 9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 563,3 |

| | | | |
|---|---|---|---|
| 2-4 |  | 3-(clorometil)-9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-amina | 610,2 |
| 2-5 |  | 3-[(4-metilpiperazin-1-il)metil]-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 675,4 |
| 2-6 |  | 2-({[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-il]metil}amino)etanol | 636,3 |

ESQUEMA 3




8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-

3-ol (**3-8**)

ETAPA A: (2-cloro-3-formilpiridin-4-il)carbamato de terc-butilo (**3-1**)

Una solución de 4-amino-2-cloropiridina (1,28 gm, 10 mmol) y dicarbonato de di-terc-butilo (2,21 gm, 10,1 mmol) en THF (20 ml) se enfrió a 0°C y se añadió lentamente una solución de bis(trimetilsilil)amida de litio 1M en THF ( 20 ml, 20 mmol) manteniendo la temperatura por debajo de 0°C. La reacción se dejó calentar a temperatura ambiente durante una hora y después se desactivó mediante la adición de cloruro de amonio acuoso 1,5 N (15 ml). Después de agitar durante varias horas la reacción se extrajo en acetato de etilo, se lavó con salmuera, la fase orgánica se secó ($Na_2SO_4$), se filtró y se evaporó. El residuo se trituró con éter dietílico dando (2-cloropiridin-4-il)carbamato de terc-butilo puro. Las aguas madres se cromatografiaron en gel de sílice eluyendo con acetato de etilo al 25 – 45%/hexano proporcionando más producto.

Se enfrió una solución de (2-cloropiridin-4-il)carbamato de terc-butilo (1,14 gm, 5 mmol) en THF seco (20 ml) a -70°C bajo una atmósfera inerte y se añadió lentamente t-butillitio 1,7 M/pentano (8 ml, 13,5 mmol). La reacción se agitó durante dos horas y después se añadió DMF seco (1,2 ml, 15,5 mmol). La reacción se dejó calentar lentamente a temperatura ambiente durante un periodo de tres horas. La mezcla de reacción se desactivó con HCl 3 N (12 ml) y se diluyó con éter dietílico. La fase éter se lavó con $NaHCO_3$ acuoso, se secó (sobre $Na_2SO_4$), se filtró y se evaporó. El residuo se trituró con éter dietílico frío dando (2-cloro-3-formilpiridin-4-il)carbamato de t-butilo puro. Las aguas madres se cromatografiaron en gel de sílice eluyendo con acetato de etilo al 15-20%/hexano dando producto adicional. RMN $^1H$ (500 MHz, $CDCl_3$): δ 11,0 (1H, s a), 10,52 (1H, s), 8,38 (1H, d, J= 6 Hz), 8,31 (1H, d, J= 6 Hz), 1,54 (9H, s); m/e (m+1): 257,2.

ETAPA B: 1-[4-(1,3-dioxolan-2-il)fenil]-2-feniletanona (**3-2**)

A una solución de 4-cianobenzaldehído (20,0 g, 152,5 mmol) y etilenoglicol (25,5 ml, 457,5 mmol) en tolueno (250 ml) se añadió ácido p-toluenosulfónico (300 mg). El matraz se equipó con una trampa de Dean-Stark y la mezcla se calentó a reflujo. Después de 5 horas la mezcla se concentró. El residuo se tomó en acetato de etilo y se lavó con $NaHCO_3$ saturado, agua (2x), y salmuera. La fase orgánica se secó ($MgSO_4$), se filtró, y se concentró dando 4-(1,3-dioxolan-2-il)benzonitrilo como un aceite transparente el cual solidificó bajo vacío: RMN $^1H$ (500 MHz, $CDCl_3$): δ 7,67 (2 H, d, J = 8,06 Hz), 7,59 (2 H, d, J = 8,30 Hz), 5,85 (1H, s), 4,13-4,05 (4H, m).

A una solución de 4-(1,3-dioxolan-2-il)benzonitrilo (5,0 g, 28,54 mmol) en THF anhidro (100 ml) se añadió cloruro de bencilmagnesio (36 ml, solución al 20% en peso en THF, 43 mmol) lentamente a 0°C. Después de una hora la mezcla se calentó a temperatura ambiente. Después de cuatro horas la mezcla se enfrió a 0°C y se desactivó con $NH_4Cl$ saturado. La mezcla se calentó a temperatura ambiente y se extrajo con acetato de etilo (3x). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y se concentraron. La cromatografía en columna ultrarrápida (acetato de etilo al 10%/hexanos) dio 1-[4-(1,3-dioxolan-2-il)fenil]-2-feniletanona como un sólido amarillo pálido: RMN $^1H$ (500 MHz,

$CDCl_3$): δ 8,02 (2 H, d, J = 8,30 Hz,), 7,57 (2 H, d, J = 8,30 Hz,), 7,38-7,24 (%H, m), 5,86 (1H, s), 4,29 (2H, s), 4,28-4,09 (4H, m).

ETAPA C: 5-cloro-2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6] naftiridina (**3-3**)

A una solución de (2-cloro-3-formilpiridin-4-il)carbamato de terc-butilo (**3-1**, 30,5 g, 118,9 mmol) y 1-[4-(1,3-dioxolan-2-il)fenil]-2-feniletanona (**3-2**, 29,0 g, 108,1 mmol) en THF anhidro (300 ml) a temperatura ambiente se añadió LHMDS (1M en THF, 248 ml) en una corriente. La mezcla de reacción se agitó a temperatura ambiente durante toda una noche y después se sometió a reflujo durante 24 horas. Se enfrió y concentró hasta un jarabe y se trató con $NaHCO_3$ (saturado, 50 ml) y agua (300 ml) formando un sólido el cual se recogió por medio de filtración. El sólido se secó, se lavó con éter y adicionalmente se secó con tolueno azeotrópicamente dando el compuesto del título. LREM m/z (M+1) Calcd.: 389,1, hallado 389,1.

ETAPA D: [2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6]naftiridin-5-il]-hidrazina (**3-4**)

Una suspensión de 5-cloro-2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6]naftiridina (**3-3**, 5,2 g, 13,4 mmol) e hidrazina anhidra (5 ml) en 1,4-dioxano anhidro (15 ml) se calentó a 100°C en un reactor de microondas durante 5 min. La mezcla de reacción se enfrió, se concentró y se secó con tolueno azeotrópicamente dando el compuesto del título como un sólido. LREM m/z (M+1) Calcd.: 385,2, hallado 385,3.

ETAPA E: 8-(4-[1,3]dioxolan-2-il-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol (**3-5**)

A una solución de [2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6]naftiridin-5-il]-hidrazina (**3-4**, 5,3 g, 13,8 mmol) en $CH_2Cl_2$ (anhidro, 40 ml) a 0°C se añadió trietilamina (9,7 ml, 68,9 mmol) seguida por una adición rápida de fosgeno en tolueno (2M, 7,6 ml). Después de agitar durante 10 minutos a temperatura ambiente, la mezcla se concentró y se añadió agua (30 ml). El sólido se recogió y se secó con tolueno azeotrópicamente dando el compuesto del título el cual se usó para la siguiente etapa sin purificación adicional. LREM m/z (M+1) Calcd.: 411,1, hallado 411,2.

ETAPA F: 4-(3-hidroxi-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)- benzaldehído (**3-6**)

Una suspensión de 8-(4-[1,3]dioxolan-2-il-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol (**3-5**, 2,7 g, 6,6 mmol) en dioxano (20 ml) y HCl 2N (20 ml) se agitó a temperatura ambiente durante 20 min. Se concentró eliminando la mayoría del dioxano a 25°C. El residuo se vertió en agua enfriada en hielo dando un sólido marrón el cual se recogió por medio de filtración y se secó con tolueno azeotrópicamente dando el compuesto del título. LREM m/z (M+1) Calcd.: 367,1, hallado 367,1.

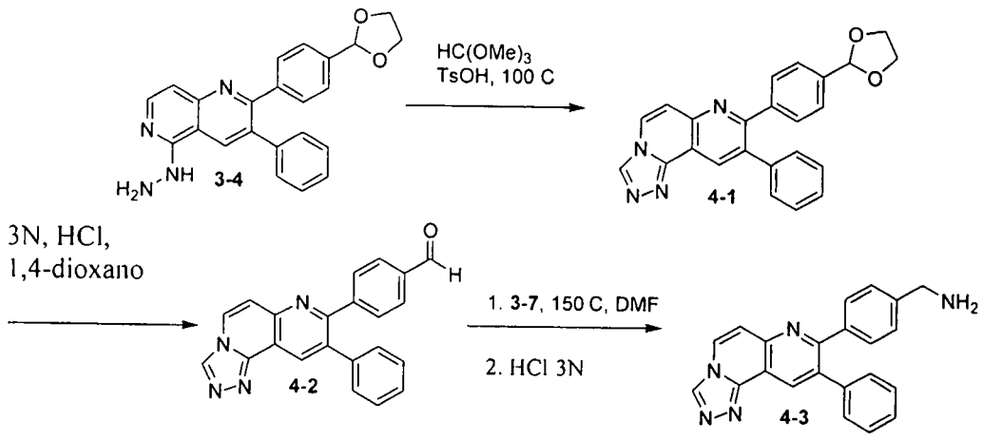
ETAPA G: 8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol (**3-8**)

Se calentó una suspensión de 4-(3-hidroxi-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-benzaldehído (**3-6**, 2,4 g, 6,6 mmol) y ácido 2-amino-2,4-dimetilpentanoico (**3-7**, 1,9 g, 13,1 mmol) en

DMF (25 ml) a 150°C durante 20 min. La mezcla de reacción se enfrió, se diluyó con dioxano (50 ml) y HCl 2N (50 ml) y se calentó a 100°C durante 30 minutos. La mezcla se enfrió y purificó por medio de HPLC de fase reversa (acetonitrilo al 0-60%/agua) dando, tras evaporación del disolvente, el compuesto del título como un sólido amarillo. HREM m/z (M+1) Calcd.: 368,1506, hallado 368,1504.

RMN-$^1$H ($CD_3OD$) δ 8,72 (s, 1 H), 7,98 (d, 1 H), 7,52 (d, 2 H), 7,46(d, 2 H), 7,24-7,38(m, 5 H), 7,12 (d, 1 H), 4,14 (s, 2 H).

ESQUEMA 4




1-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil] metanamina (**4-3**)

ETAPA A: 8-[4-(1,3-dioxolan-2-il)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**4-1**)

A una solución de [2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6]naftiridin-5-il]-hidrazina (**3-4**, 1,6 g, 4,2 mmol) y monohidrato de ácido toluenosulfónico (79 mg, 0,4 mmol) en tolueno:MeOH 3:1 (16 ml) se añadió trimetilortoformiato (0,58 ml, 12,5 mmol). La mezcla se calentó a 100°C en un reactor de microondas durante 1 hora. La mezcla de reacción se concentró después *a vacío*. El sólido se recogió y se secó con tolueno azeotrópicamente dando el compuesto del título el cual se usó para la siguiente etapa sin purificación adicional. LREM m/z (M+1) Calcd.: 395,1, hallado 395,2.

ETAPA B: 4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il) benzaldehído (**4-2**)

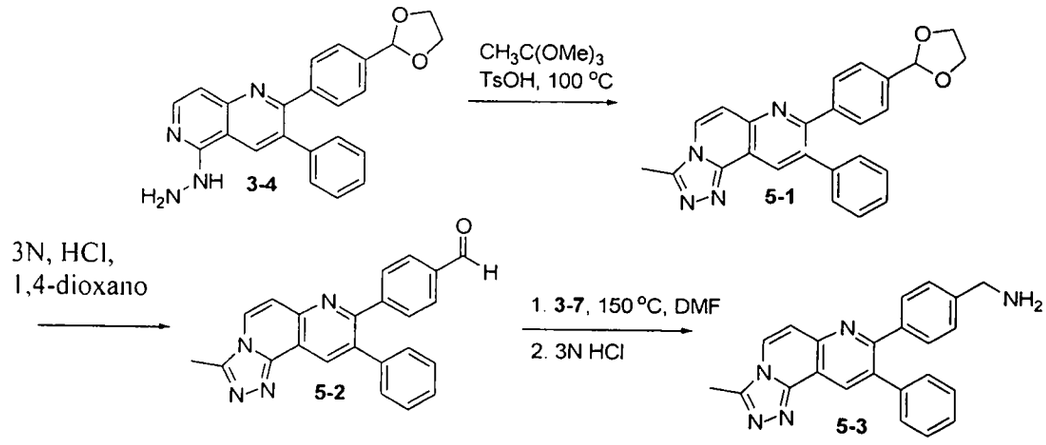
Se agitó una suspensión de 8-[4-(1,3-dioxolan-2-il)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**4-1**, 0,80 g, 2,0 mmol) en dioxano (10 ml) y HCl 3N (10 ml) a temperatura ambiente durante 15 min. La mezcla se concentró a 25°C eliminando la mayoría del dioxano. El residuo se vertió en agua enfriada en hielo dando un sólido marrón el cual se recogió mediante filtración y se secó con tolueno (x2) azeotrópicamente dando el compuesto del título. LREM m/z (M+1) Calcd.: 351,1, hallado 351,2.

ETAPA C: 1-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]

metanamina (**4-3**)

Se calentó una suspensión de 4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)benzaldehído (**4-2**, 0,80 g, 2,3 mmol) y ácido 2-amino-2,4-dimetilpentanoico (**3-7**, 0,340 g, 2,3 mmol) en DMF (10 ml) a 150°C durante 30 min. La mezcla de reacción se enfrió y el disolvente se eliminó *a vacío*. El residuo en bruto se disolvió en HCl 3N (8 ml) y se calentó a 100°C durante 30 min. La mezcla se enfrió y purificó por medio de HPLC de fase reversa (acetonitrilo al 5-65%/agua durante 15 minutos) dando, tras evaporación de los disolventes, el compuesto del título como un sólido amarillo. RMN-$^1$H ($CD_3OD$) δ 9,60 (s, 1 H), 8,98 (s, 1 H), 8,73 (d, 1 H), 7,75 (d, 1 H), 7,60 (d, 2 H), 7,46 (d, 2 H), 7,39-7,36 (m, 5 H), 4,15 (s, 2H).

ESQUEMA 5




4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina (**5-3**)

ETAPA A: 8-[4-(1,3-dioxolan-2-il)fenil]-3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**5-1**)

A una solución de [2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6]naftiridin-5-il]-hidrazina (**3-4**, 0,35 g, 0,91 mmol) y monohidrato de ácido toluenosulfónico (17 mg, 0,09 mmol) en tolueno:MeOH 3:1 (4 ml) se añadió trimetilortoacetato (0,157 ml, 1,23 mmol). La mezcla se calentó a 100°C en un reactor de microondas durante 75 horas. La mezcla de reacción se concentró después *a vacío*. El sólido se recogió y se secó con tolueno azeotrópicamente dando el compuesto del título el cual se usó para la siguiente etapa sin purificación adicional. LREM m/z (M+1) Calcd.: 409,2, hallado 409,2.

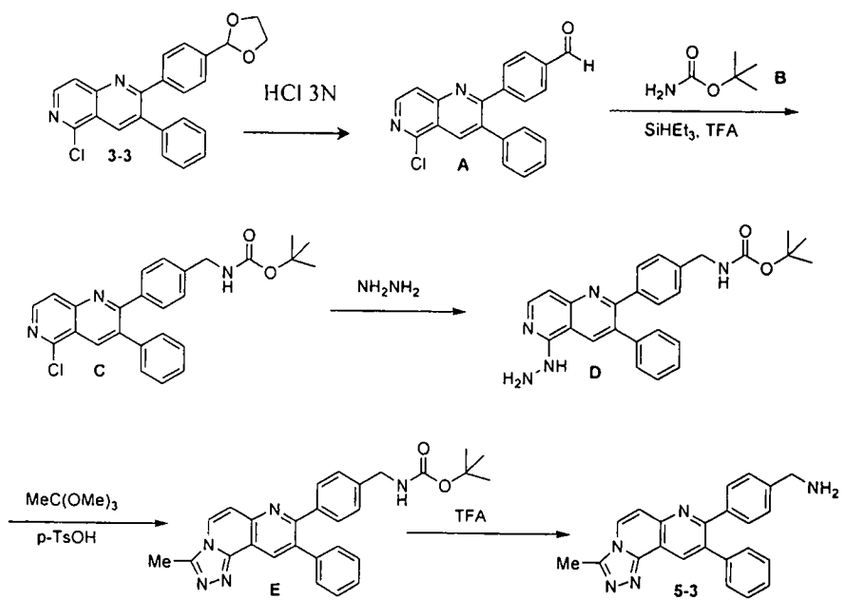
ETAPA B: 4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il) Benzaldehído (**5-2**)

Se agitó una suspensión de 8-[4-(1,3-dioxolan-2-il)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**5-1**, 0,80 g, 2,0 mmol) en dioxano (5 ml) y HCl 3N (5 ml) a temperatura ambiente durante 15 min. La mezcla se concentró a 25°C eliminando la mayoría del dioxano. El residuo se vertió en agua enfriada en hielo dando un sólido marrón el cual se recogió mediante filtración y se secó con tolueno (x2) azeotrópicamente dando el compuesto del título. LREM m/z (M+1) Calcd.: 365,1, hallado 365,2.

ETAPA C: 4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina (**5-3**)

Se calentó una suspensión de 4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)benzaldehído (**13**, 0,25 g, 0,69 mmol) y ácido 2-amino-2,4-dimetilpentanoico (**3-7**, 0,101 g, 0,69 mmol) in DMF (3 ml) a 150°C durante 30 min. La mezcla de reacción se enfrió y el disolvente se eliminó *a vacío*. El residuo en bruto se disolvió en HCl 3N (2,5 ml) y se calentó a 100°C durante 30 min. La mezcla se enfrió y purificó por medio de HPLC de fase reversa (acetonitrilo al 5-65%/agua durante 15 minutos) dando, tras evaporación de los disolventes, el compuesto del título como un sólido amarillo. HREM m/z (M+1) Calcd.: 366,1713, hallado 366,1715.

ESQUEMA 5 (SÍNTESIS ALTERNA)




4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencil amina (**5-3**)

ETAPA A: 4-(5-cloro-3-fenil-[1,6]naftiridin-2-il)-benzaldehído (**A**)

A una solución de **3-3** (5,0 g, 12,9 mmol) en 1,4-dioxano (30 ml) a 0°C se añadieron 8,5 ml de HCl 3N (25,7 mmol). La mezcla se dejó calentar hasta temperatura ambiente y se agitó durante 1,3 hr. La reacción se desactivó mediante $NaHCO_3$ (sat.) hasta pH=7-8. La mezcla se extrajo mediante EtOAc (x3). Las fases orgánicas combinadas se lavaron con salmuera y se secaron sobre $MgSO_4$ y se concentraron proporcionando un sólido amarillo como el producto **A** deseado. CL/EM hallado: M+1= 345,1

ETAPA B: ácido [4-(5-cloro-3-fenil-[1,6]naftiridin-2-il)-bencil]-carbámico de *terc*-butilo éster (**C**)

A una solución de **A** (2,8 g, 8,1 mmol) y **B** (1,1g, 8,9 mmol) en 15 ml de MeCN anhidro se añadió trietilsilano (8,5 g, 73 mmol) seguido por ácido trifluoroacético (3,7 g, 32,5 mmol). La mezcla

se agitó a temperatura ambiente durante 3 horas. La mezcla se vertió después en solución de bicarbonato de sodio acuoso (30 ml) y se extrajo mediante EtOAc (x3). Las fases orgánicas combinadas se lavaron mediante salmuera y se secaron sobre $MgSO_4$. Tras la eliminación del solvente, el residuo se purificó por medio de cromatógrafo de columna ultrarrápida proporcionando el producto deseado **C**. CL/EM hallado: M+1= 446,1

ETAPA C: ácido [4-(5-cloro-3-fenil-[1,6]naftiridin-2-il)-bencil]-carbámico de *terc*-butilo éster (**D**)

A una solución de **C** (3,7 g, 8,3 mmol) en 22 ml de 1,4-dioxano se añadió hidrazina (6,1 g, 189,1 mmol) gota a gota. La mezcla se calentó a 100°C en un reactor de microondas durante 5 minutos. Tras la eliminación del disolvente, el residuo se llevó en EtOAc y se lavó con solución de $NaHCO_3$ saturada. La fase orgánica se lavó mediante salmuera y se secó sobre $MgSO_4$ y se concentró proporcionando el producto **D** deseado, el cual se usó en la siguiente etapa sin purificación adicional. CL/EM hallado: M+1= 442,2

ETAPA D: [4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencil]- éster *terc*-butílico de ácido carbámico (**E**)

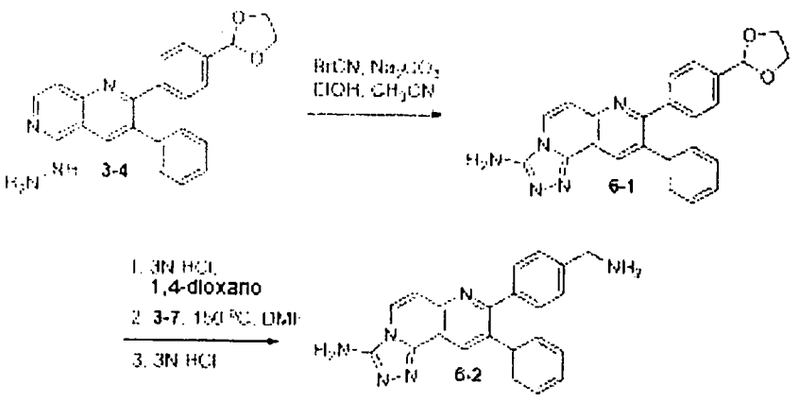
A una disolución de **D** (3,8 g, 8,6 mmol) y ácido *p*-toluenosulfónico monohidrato (0,08 g, 0,4 mmol) en 20 ml de tolueno/metanol (3:1) se añadió ortoacetato de trimetilo (1,4 g, 11,6 mmol). La solución se calentó en reactor de microondas a 100°C durante 35 minutos. La reacción se desactivó mediante $NaHCO_3$ sólido (0,5 g). La fase orgánica se concentró y purificó en cromatógrafo de columna ultrarrápida (EtOAc al 10%-MeOHal 10%/EtOAc al 90% durante 35 minutos) proporcionando el producto deseado **E**.
CL/EM hallado: M+1= 466,2

ETAPA E: 4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina (**5-3**)

A una solución de **E** (4,1g, 8,7 mmol) en 80 ml de $CH_2Cl_2$ se añadieron 40 ml de TFA gota a gota. La mezcla se agitó a temperatura ambiente durante 15 minutos. El disolvente se eliminó. El residuo se trató con $NaHCO_3$ (sat.) hasta pH=9. La mezcla se extrajo mediante EtOAc (x6). Las fases orgánicas combinadas se concentraron y se secaron sobre $MgSO_4$. Tras la eliminación del disolvente, se obtuvo el producto deseado **5-6** un sólido amarillo. CL/EM hallado: M+1= 366,1
RMN-$^1$H ($CD_3OD$) δ 8,95 (s, 1 H), 8,66 (d, 1 H), 7,82 (d, 1 H), 7,60 (d, 2 H), 7,45 (d, 2 H), 7,42-7,34 (m, 5 H), 4,15 (s, 2H), 3,00 (s, 3 H).

-220

ESQUEMA 6




8-[4-(aminometil)fenil]-9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**6-2**)

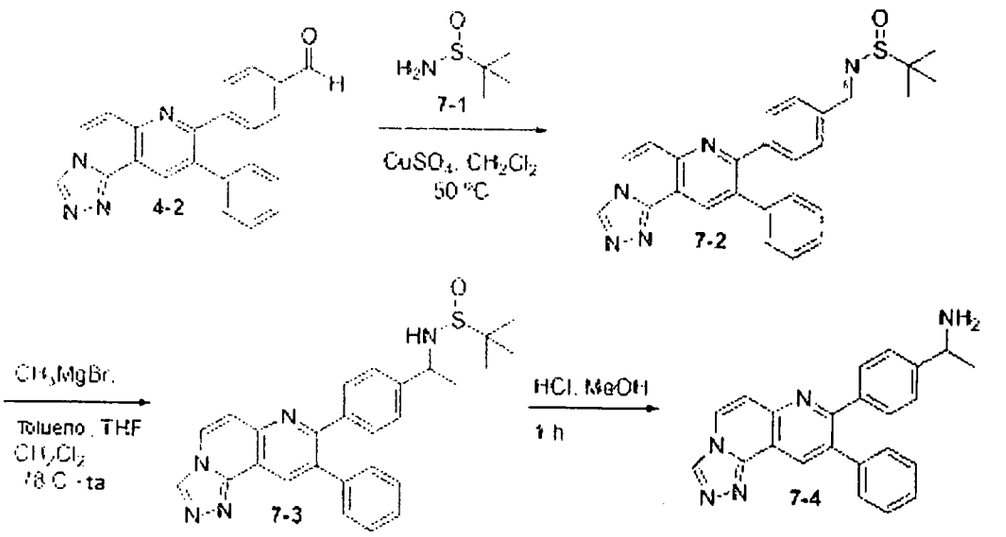
ETAPA A: 8-[4-(1,3-dioxolan-2-il)-fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**6-1**)

A EtOH seco (1 ml) se añadió bromuro de cianógeno (0,104 ml, 0,52 mmol, 5M en MeCN) seguido por carbonato de sodio (96 mg, 0,91 mmol). Se añadió [2-(4-[1,3]dioxolan-2-il-fenil)-3-fenil-[1,6]naftiridin-5-il]-hidrazina (**3-4**, 100 mg, 0,26 mmol) y la mezcla se agitó durante 3 horas. La mezcla de reacción se concentró *a vacío* y el sólido resultante se usó sin purificación adicional. LREM m/z (M+1) Calcd.: 410,2, hallado 410,1.

ETAPA B: 8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-f][1,6]naftiridin-3-ol (**6-2**)

El compuesto del título se preparó a partir de 8-[4-(1,3-dioxolan-2-il)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina (**6-1**) usando los procedimientos descritos en el esquema 5 (**5-1** a **5-3**). LREM m/z (M+1) Calcd.: 367,2, hallado 367,1.

ESQUEMA 7




1-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil] etanamina (7-4)

ETAPA A: 2-metil-N-{(1E)-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metilideno}propano-2-sulfinamida (7-2)

Se agitaron 2-metil-2-propano-sulfinamida (**7-1**, 647 mg, 5,3 mmol), sulfato cúprico (1,70 g, 7,30 mmol), y aldehído **4-2** (511 mg, 1,45 mmol) en cloruro de metileno (10 ml) durante 5 días a 50°C. Después de enfriar a temperatura ambiente, la mezcla se filtró a través de celite, se concentró a un volumen mínimo y se purificó por medio de cromatografía en gel de sílice automatizada (MeOH al 0-10% en $CH_2Cl_2$ durante 30 minutos) dando el compuesto del título como una espuma marrón. LREM m/z (M+1) Calcd.: 454,2, hallado 454,2.

ETAPA B: 2-metil-N-{1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etil}propano-2-sulfinamida (7-3)

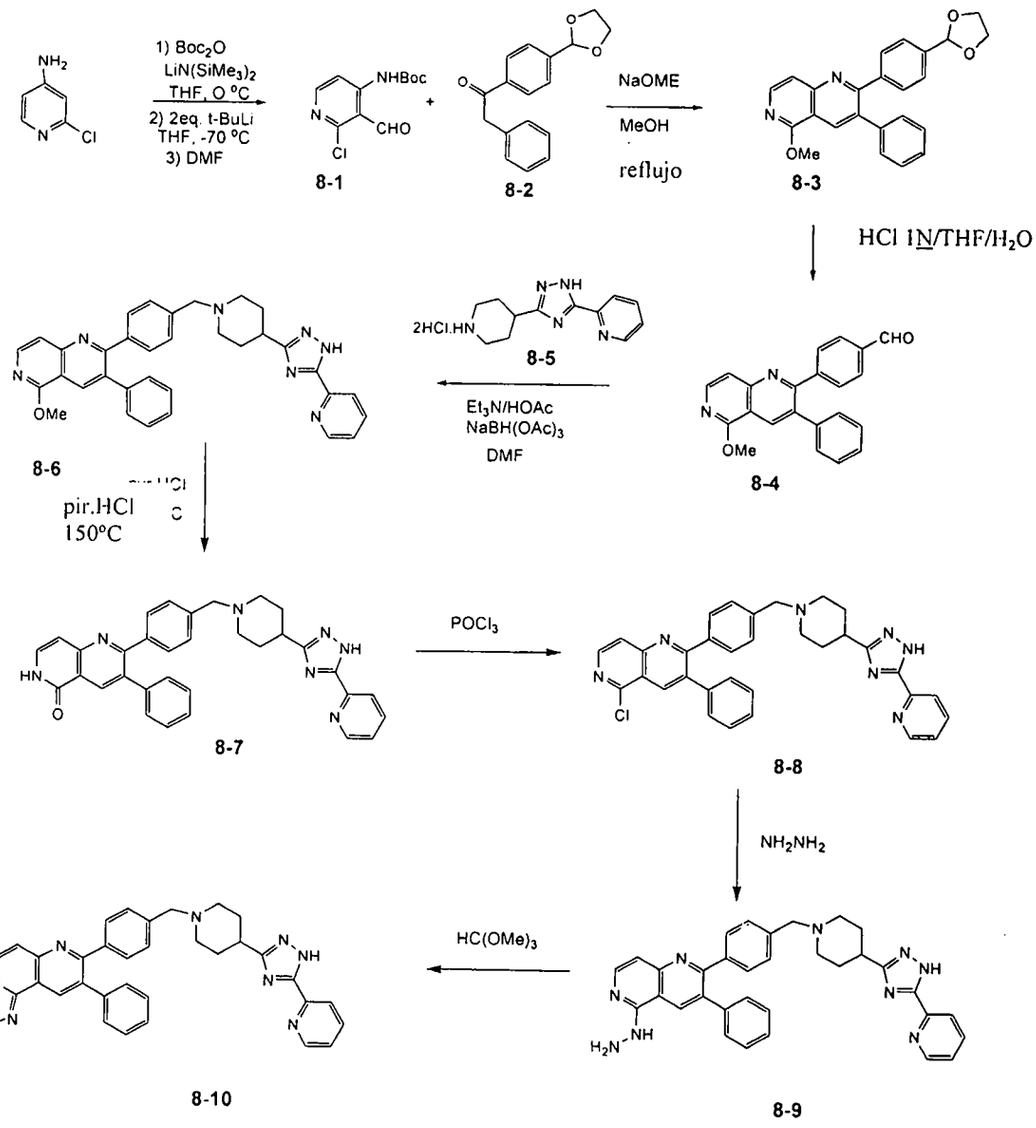
Se añadió solución de bromuro de metilmagnesio (13,5 ml de solución 1,4 M en tolueno/THF 3:1, 19 mmol) a una solución agitada de 2-metil-N-{(1E)-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metilideno}propano-2-sulfinamida (**7-2**, 298 mg, 0,66 mmol) en cloruro de metileno (5 ml) a -78°C y la solución se calentó a ta. Después de 18 horas, la reacción se desactivó con solución de cloruro de amonio saturada y se extrajo con acetato de etilo, se lavó con salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró dando una espuma ambarina, la cual se purificó por medio de cromatografía en gel de sílice (MeOH al 0-10%/$CH_2Cl_2$ durante 30 minutos) dando el compuesto del título como una espuma amarilla.

LREM m/z (M+1) Calcd.: 470,2, hallado 470,3.

ETAPA C: 1-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina (7-4)

A una solución agitada de 2-metil-N-{1-[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etil}propano-2-sulfinamida (**7-3**, 180 mg, 0,38 mmol) en metanol (6 ml) se añadió HCl conc. (1,5 ml ). Después de 1 hora, se añadió agua y la mezcla se lavó con cloruro de metileno. La parte acuosa se basificó con solución de carbonato de sodio saturada y se extrajo con cloruro de metileno. Se añadió HCl 2N (5 ml) a la fase orgánica y la mezcla se concentró a un volumen mínimo. El producto en bruto se purificó usando la HPLC preparativa en fase reversa dando el compuesto del título como un sólido amarillo pálido. LREM m/z (M+1) Calcd.: 366,2, hallado 366,3.

ESQUEMA 8



9-fenil-8-{4-{[4-(5-piridin-2-il-4*H*-1,2,4-triazol-3-il)-piperidin-1-il]metil}fenil}-[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**8-10**)

(2-cloro-3-formilpiridin-4-il)carbamato de terc-butilo (**8-1**)

Una solución de 4-amino-2-cloropiridina (1,28 gm, 10 mmol) y dicarbonato de di-terc-butilo (2,21 gm, 10,1 mmol) en THF (20 ml) se enfrió a 0°C y se añadió una solución de bis(trimetilsilil)amida de litio 1M en THF (20 ml, 20 mmol) manteniendo lentamente la temperatura por debajo de 0°C. La reacción se dejó calentar a temperatura ambiente durante una hora y después se desactivó mediante la adición de cloruro de amonio acuoso 1,5 N (15 ml). La mezcla se extrajo dentro de acetato de etilo, se lavó con salmuera y la fase orgánica se secó ($Na_2SO_4$), se filtró y se evaporó. El residuo se trituró con éter dietílico dando (2-cloropiridin-4-il)carbamato de terc-butilo puro. Las aguas madres se cromatografiaron en gel de sílice eluyendo con acetato de etilo al 25 – 45%/hexano proporcionando más producto.

Se enfrió una solución de (2-cloropiridin-4-il)carbamato de terc-butilo (1,14 g, 5 mmol) en THF seco (20 ml) a -70°C bajo una atmósfera inerte y se añadió lentamente t-butillitio 1,7 M/pentano (8 ml, 13,5 mmol). La reacción se agitó durante dos horas y después se añadió DMF seco (1,2 ml, 15,5 mmol). La reacción se dejó calentar lentamente a temperatura ambiente durante un periodo de tres horas. La mezcla de reacción se desactivó con HCl 3 N (12 ml) y se diluyó con éter dietílico. La fase éter se lavó con $NaHCO_3$ acuoso, se secó (sobre $Na_2SO_4$), se filtró y se evaporó. El residuo se trituró con éter dietílico frío dando (2-cloro-3-formilpiridin-4-il)carbamato de t-butilo puro. Las aguas madres se cromatografiaron en gel de sílice eluyendo con acetato de etilo al 15-20%/hexano dando producto adicional. RMN $^1H$ (500 MHz, $CDCl_3$): δ 11,0 (1H, s a), 10,52 (1H, s), 8,38 (1H, d, J= 6 Hz), 8,31 (1H, d, J= 6 Hz), 1,54 (9H, s); m/e (m+1): 257,2.

1-[4-(1,3-dioxolan-2-il)fenil]-2-feniletanona (**8-2**)

A una solución de 4-cianobenzaldehído (20,0 g, 152,5 mmol) y etilenglicol (25,5 ml, 457,5 mmol) en tolueno (250 ml) se añadió ácido p-toluenosulfónico (300 mg). El matraz se equipó con una trampa de Dean-Stark y la mezcla se calentó a reflujo. Después de 5 horas la mezcla se concentró. El residuo se tomó en acetato de etilo y se lavó con $NaHCO_3$ saturado, agua (2x), y salmuera. La fase orgánica se secó ($MgSO_4$), se filtró, y se concentró dando 4-(1,3-dioxolan-2-il)benzonitrilo como un aceite transparente el cual solidificó bajo vacío: RMN $^1H$ (500 MHz, $CDCl_3$): δ 7,67 (2 H, d, J = 8,06 Hz), 7,59 (2 H, d, J = 8,30 Hz), 5,85 (1H, s), 4,13-4,05 (4H, m).

A una solución de 4-(1,3-dioxolan-2-il)benzonitrilo (5,0 g, 28,54 mmol) en THF anhidro (100 ml) se añadió cloruro de bencilmagnesio (36 ml, solución al 20% en peso en THF, 43 mmol) lentamente a 0°C. Después de una hora la mezcla se calentó a temperatura ambiente. Después de cuatro horas la mezcla se enfrió a 0°C y se desactivó con $NH_4Cl$ saturado. La mezcla se calentó a temperatura ambiente y se extrajo con acetato de etilo (3x). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y se concentraron. La cromatografía en columna ultrarrápida (acetato de etilo al 10%/hexanos) dio 1-[4-(1,3-dioxolan-2-il)fenil]-2-feniletanona como un sólido amarillo pálido: RMN $^1H$ (500 MHz,

$CDCl_3$): δ 8,02 (2 H, d, J = 8,30 Hz,), 7,57 (2 H, d, J = 8,30 Hz,), 7,38-7,24 (5H, m), 5,86 (1H, s), 4,29 (2H, s), 4,28-4,09 (4H, m).

2-[4-(1,3-dioxolan-2-il)fenil]-5-metoxi-3-fenil-1,6-naftiridina (**8-3**)

A una solución parcial de 1-[4-(1,3-dioxolan-2-il)fenil]-2-feniletanona (997 mg, 3,72 mmol) y (2-cloro-3-formilpiridin-4-il)carbamato de terc-butilo (924 mg, 3,6 mmol) en metanol seco (14 ml) se añadió metóxido de sodio al 25% en peso/metanol (2,5 ml, 11,4 mmol). La mezcla de reacción se calentó a 65°C durante cuatro horas. La reacción enfriada se concentró eliminando el metanol y el residuo se fraccionó entre agua y acetato de etilo. La fase orgánica se secó ($Na_2SO_4$), se filtró y se evaporó. El residuo se trituró con éter frío dando 2-[4-(1,3-dioxolan-2-il)fenil]-5-metoxi-3-fenil-1,6-naftiridina pura. Las aguas madres se purificaron mediante cromatografía en gen de sílice y la elución con acetato de etilo al 20-40%/hexano dio producto adicional. RMN $^1H$ (500 MHz, $CDCl_3$): δ 8,54 (1H, s), 8,23 (1H, d, J=5,9 Hz), 7,55 (1H, d, J= 5,40 (2H, d, J=8 Hz), 7,29-7,30 (3H, m), 7,22-7,25 (2H, m), 4,16 (3H, s), 4,02-411 (4H, 2 m). m/e (m+1): 385,1.

4-(5-metoxi-3-fenil-1,6-naftiridin-2-il)benzaldehído (**8-4**)

A una solución de 2-[4-(1,3-dioxolan-2-il)fenil]-5-metoxi-3-fenil-1,6-naftiridina (760 mg, 1,98 mmol) en THF (8 ml) se añadió HCl 1 N (6 ml) y la solución se agitó durante tres horas. Se añadió acetato de etilo y la mezcla se hizo básica con $Na_2CO_3$ acuoso. La fase orgánica se secó ($Na_2SO_4$), se filtró y el disolvente se evaporó. El residuo se trituró con éter dietílico dando productos puros. Las aguas madres se purificaron mediante cromatografía en columna en gen de sílice y la elución con acetato de etilo al 10-30%/hexano dio producto adicional. RMN $^1H$ (500 MHz, $CDCl_3$): δ 10,10 (1H, s), 8,60 (1H, s), 8,26 (1H, d, J= 6 Hz), 7,81 (2H, d, J=8,3Hz), 7,62 (2H, d, J=8,3Hz), 7,56 (1H, d, J=6.1Hz), 7,30-7,32 (3H, m), 7,21-7,23 (2H, m), 4,17 (3H, s). m/e (m+1): 341,1.

Diclorhidrato de 2-(3-piperidin-4-il-1H-1,2,4-triazol-5-il)piridina (**8-5**)

Se añadió carbonildiimidazol (3,57 g, 22 mmol) a una solución de ácido 1-(terc-butoxicarbonil)-piperidina-4-carboxílico (4,59 g, 20 mmol) en cloruro de metileno (50 ml) y se agitó durante dos horas hasta que cesó la evolución gaseosa. Después se añadió hidrazina (0,8 ml, ~26 mmol) a la reacción y la reacción se agitó a temperatura ambiente durante otras dos horas. La reacción se diluyó con más cloruro de metileno y se lavó con $NaHCO_3$ acuoso saturado. La fase orgánica se secó sobre $Na_2SO_4$ anhidro, se filtró y el disolvente se evaporó dando un residuo viscoso. La trituración con éter dietílico proporcionó 4-(hidrazinocarbonil)-piperidina-1-carboxilato de terc-butilo como un sólido blanquecino. RMN $^1H$ (500 MHz, $CDCl_3$): δ 6,77 (1H, s a), 4,15 (2H, s a), 3,90 (2H, v s a), 2,75 (2H, s a), 2,22 (1H, m), 1,78 (2H, d a, J=11,9 Hz), 1,66 (2H, q a, J=12,2 Hz, J=27,5 Hz), 1,47 (9H, s).

Este material (2,43 g, 10 mmol) se disolvió en 2-etoxietanol anhidro (20 ml) y se añadió 2-cianopiridina (1,14 g, 11 mmol) a la solución. Después de que se añadió metóxido sódico al 25% en peso/metanol (1,1 ml, ~5 mmol) la mezcla se calentó a 130°C durante 16 horas. La reacción enfriada se neutralizó con ácido acético y se fraccionó entre acetato de etilo y $NaHCO_3$ acuoso. La fase orgánica se secó sobre $Na_2SO_4$, las sales se eliminaron mediante filtración y el disolvente se evaporó bajo vacío.

Este residuo se trituró con éter dietílico dando 4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidina-1-carboxilato como un sólido blanco. RMN $^1$H (500 MHz, $CDCl_3$): δ 8,70 (1H, d, J= 3,9 Hz), 8,19 (1H, d, J=7 ,9Hz), 7,87 (1H, d t, J=1,7Hz, J=8Hz), 7,40 (1H, m), 4,20 (2H, s a), 3,03 (1H, m), 2,95 (2H, s a), 2,09 (2H, d a, J=12 Hz), 1,86 (2H, q a, J= 4,2Hz), 1,49 (9H, s); m/e (m+1): 330,2

Este material (2,68 g, 8,14 mmol) se suspendió en HCl 4 N/dioxano. La mezcla de reacción detenida se agitó a temperatura ambiente durante 16 horas y después se diluyó con éter dietílico. Los sólidos se aislaron mediante filtración y el sólido higroscópico se digirió en acetonitrilo. Este sólido se aisló mediante filtración y se disolvió parcialmente en metanol caliente. Tras enfriamiento y adición de algún éter etílico a la solución de 2-(3-piperidin-4-il-1H-1,2,4-triazol-5-il)piridina precipitó lentamente como la sal diclorhidrato. RMN $^1$H (500 MHz, DMSO-d6): δ 9,10 (1H, s a), 8,92 (1H, s a), 8,73 (1H, d, J=4,9Hz), 8,10-8,20 (2H, m), 7,64 (1H, t, J=5,7 Hz), 3,33 (2H, d a, J=12,7 Hz), 3,16 (1H, m), 3,05 (2H, c a, J=11,9 Hz, J=21,8 Hz), 2,18 (2H, d a, J=11,5 Hz), 1,99 (2H, c a, j=11,0 Hz, J=22,2 Hz): m/e(m+1): 230,3.

5-metoxi-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il] metil}fenil-1,6-naftiridina (**8-6**)

A un solución de diclorhidrato de 2-(3-piperidin-4-il-1H-1,2,4-triazol-5-il)piridina (542 mg, 1,80 mmol) y 4-(5-metoxi-3-fenil-1,6-naftiridin-2-il)benzaldehído (560 mg, 1,65 mmol) en DMF seco (6 ml) se añadió trietilamina ( 0,83 ml, 6 mmol). Después de agitar durante 10 minutos, se añadió ácido acético (1,03 ml, 18 mmol) y la mezcla se agitó a temperatura ambiente durante toda una noche. Después se añadió triacetoxiborohidruro de sodio (367 mg, 1,73 mmol) en una parte y se agitó durante seis horas. Después la monitorización mediante CL/EM determinó que la reacción no estaba completa, se añadieron partes adicionales de triacetoxiborohidruro de sodio (2 x 90 mg) durante las varias horas siguientes tiempo al cual se completó la reacción. La mezcla se diluyó con acetato de etilo y se añadió $Na_2CO_3$ acuoso. La fase orgánica se separó y se lavó dos veces con agua, se secó ($Na_2SO_4$) y el disolvente se evaporó. El residuo se digirió con acetonitrilo y tras enfriamiento el producto sólido se aisló mediante filtración. Este sólido se suspendió en acetato de etilo caliente y se añadió metanol lentamente hasta que la disolución se hubo completado. Los disolventes se redujeron a un volumen pequeño y se dejaron enfriar como el producto puro cristalizado aparte. Las aguas madres se purificaron mediante cromatografía en columna en gen de sílice y la elución con metanol/acetato de etilo al 10-30%/hexano dio producto adicional. RMN $^1$H (500 MHz, $CDCl_3$): δ 8,66 (1H, d, J= 4,7Hz), 8,54 (1H, s), 8,23 (1H, d, J=6 Hz), 8,16 (1H, d, J=7,8Hz), 7,83 (1H, dt, J= 1,7Hz, J=7,8 Hz), 7,56 (1H, d, J=6 Hz), 7,40 (2H, d, J= 8Hz), 7,36 (1H, dd), 7,28-7,30 (3H, m), 7,23-7,25 (2H, m), 4,16 (3H, s), 3,54 (2H, s), 2,96 (2H, d a, J= 11,5Hz), 2,85 (1H, t, J=3,7Hz), 2,06-2,17 (4H, m), 1,92-2,01(2H, m). m/e(m+1): 554,3, 277,9 [(m+2)/2].

3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridin-5(6H)-ona (**8-7**)

Se calentó una mezcla de 5-metoxi-3-fenil-2-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il] metil}fenil)-1,6-naftiridina (725 mg, 1.31 mmol) y clorhidrato de piridina (6,9 gm, ~60

mmol) a 150°C durante diez minutos. El residuo enfriado se disolvió en la cantidad mínima de agua y se neutralizó con $NaHCO_3$ acuoso. El sólido precipitado se recogió mediante filtración y se purificó mediante cromatografía en columna en gel de sílice eluyendo con metanol al 1-14%/acetato de etilo ($NH_4OH$ saturado). El producto aislado se digirió en metanol/acetonitrilo dando producto puro. RMN 1H(500 MHz, DMSO-d6): δ 11,58 (1H, d, J=4,8Hz), 8,68 (1H, s a), 8,39 (1H, s), 8,03 (1H, d, J=7,3Hz), 7,50 (2H, t, J=6,5Hz), 7,31-7,33 (5H, m), 7,24-7,25 (4H, m), 6,79 (2H, d, J=7,3Hz), 3,50 (2H, s), 2,84 (2H, d a, J=10,5Hz), 2,72 (1H, m), 2,08 (2H, t a, J=11 Hz), 1,95 (2H, d a, J=11,6Hz), 1,77 (2H, m). m/e(m+1): 540,3, 270,9 [(m+2)/2].

5-cloro-3-fenil-2-(4-{[4-(5-piridin-2-il-4*H*-[1,2,4]-triazol-3-il)piperidin-1-ilmetil]-fenil}-[1,6]-naftiridina (**8-8**)

Una mezcla de **8-7** (5,5 g, 10,2 mmol) y $POCl_3$ (50,0 g, 326,1mmol) y DMF (0,3 g, 4,1 mmol) se calentó a reflujo a 130°C durante 3 horas. La mezcla de reacción se enfrió y concentró eliminando $POCl_3$. Se añadieron 40 ml de tolueno y se concentraron obteniendo un sólido. Se añadieron al sólido 50 ml de $H_2O$ y 40 ml de $NaHCO_3$ (saturados) y 20 ml de NaOH 1N a pH=9. La mezcla se agitó precipitando en un sólido el cual se recogió por medio de filtración como el producto deseado **8-8**. Se agitó mediante agua y $CH_3CN$ y se secó bajo vacío.

CL/EM: M+1 = 559,09

(3-fenil-2-{4-[4-(5-piridin-2-il-4*H*-[1,2,4]-triazol-3-il)-piperidin-1-ilmetil]-fenil}-[1,6]-naftiridina (**8-9**)

Se calentó una suspensión de **8-8** (4,3 g, 7,7 mmol) en 30 ml de 1,4-dioxano e hidrazina (7,4 g, 231,1 mmol) en un reactor de microondas a 100°C durante 5 minutos. La mezcla de reacción se enfrió y concentró eliminando disolventes. Se añadieron 40 ml de tolueno (x3) y se retiraron a vacío retirando la hidrazina residual. El producto deseado **8-9** se obtuvo como un sólido.

CL/EM: M+1 = 554,4

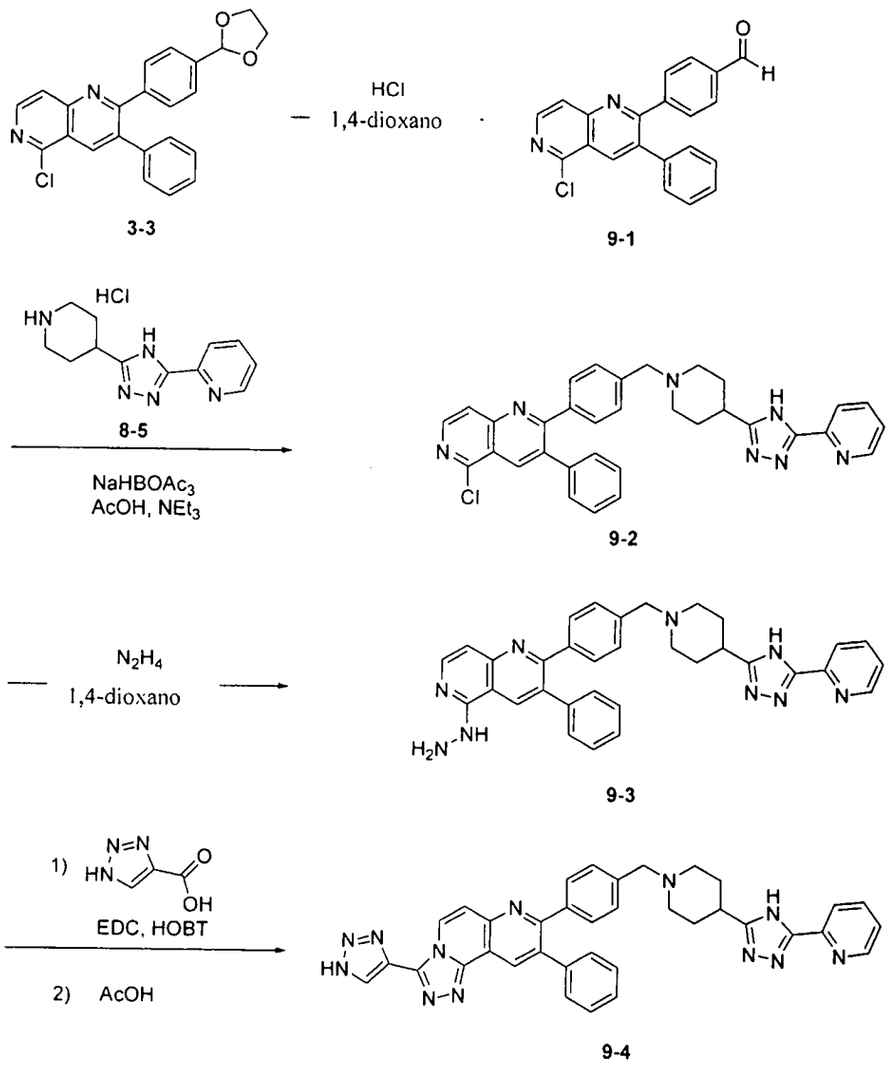
9-fenil-8-{4-{[4-(5-piridin-2-il-4*H*-1,2,4-triazol-3-il)-piperidin-1-il]metil}fenil}-[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina (**8-10**)

A una solución de **8-9** (4,5 g, 8,1 mmol) en 20 ml de metanol y 60 ml de tolueno se añadió trimetoxiortoformiato (3,5 g, 32,5 mmol) y ácido toluenosulfónico (0,1 g, 0,8 mmol). La mezcla se sometió a reflujo durante 10 horas. Tras la eliminación del disolvente, el residuo se purificó mediante cromatografía en columna ultrarrápida ($CHCl_3$ al 100%-$CHCl_3$ al 50% y metanol al 50%) proporcionando el producto deseado **8-10**.

HREM: M+1 (cal) =564,2619; hallado = 564,2589

RMN $^1H$ (500 MHz, $CD_3OD$): δ 9,35 (1H, s), 8,96 (1H, s), 8,72 (1H, d), 8,59 (1H, d), 8,28-8,10 (2H, m), 7,68-7,48 (6H, m), 7,40-7,30 (5H, m), 4,40 (2H, s), 3,68-3,20 (5H, m), 2,50-2,10 (4H, m).

ESQUEMA 9




9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-4**)

4-(5-cloro-3-fenil-1,6-naftiridin-2-il)benzaldehído (**9-1**)

A una solución agitada de **3-3** (16 g, 41,1 mMol) en 1,4-dioxano anhidro (75 ml) a 0°C se añadió HCl 3N (27 ml). La reacción se dejó después alcanzar la temperatura ambiente y se agitó durante alrededor de 3 horas. Tras la completación, la reacción se desactivó con $NaHCO_3$ saturado alcanzando un pH de >7. El producto se extrajo en acetato de etilo (3 x 150 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron con $Na_2SO_4$ y $MgSO_4$, se filtraron y se concentraron *a vacío* proporcionando 4-(5-cloro-3-fenil-1,6-naftiridin-2-il)benzaldehído **9-1** como un sólido canela. CL/EM (M+1) calculado: 345,8; observado: 345,0.

5-hidrazino-3-fenil-2-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)-1,6-naftiridina (**9-2**)

A una solución agitada de **9-1** (4,9 g, 14,2 mMol) y **8-5** (4,2 g, 15,6 mMol) en NMP (50 ml) se añadió trietilamina (6 ml, 42,6 mMol) seguida por ácido acético (1,6 ml, 28,4 mMol). Después de agitar a temperatura ambiente durante toda una noche, se añadió triacetoxiborohidruro de sodio (3,6 g, 17 mMol) por partes. Tras completación, la reacción se diluyó con acetato de etilo y se lavó con $NaHCO_3$ saturado, seguido por agua, después salmuera. La fase orgánica se secó con $Na_2SO_4$ y $MgSO_4$, se filtró y se concentró *a vacío*. El residuo en bruto se purificó usando cromatografía ultrarrápida en sílice (gradiente: MeOH 0% to 10% MeOH in $CHCl_3$ durante 25 minutos) proporcionando **9-2** como un sólido naranja. CL/EM (M+1) calculado: 559,1; observado: 559,2

5-hidrazino-3-fenil-2-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)-1,6-naftiridina (**9-3**)

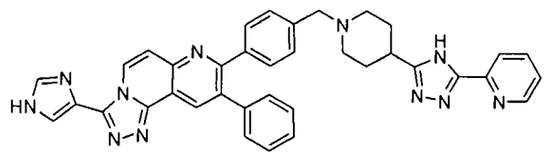
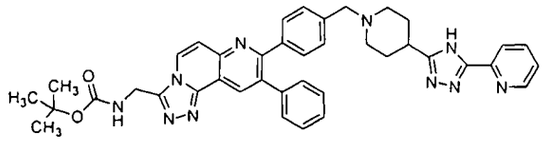
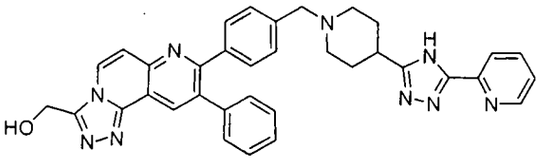
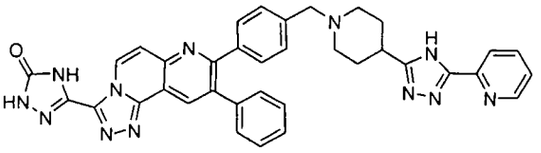
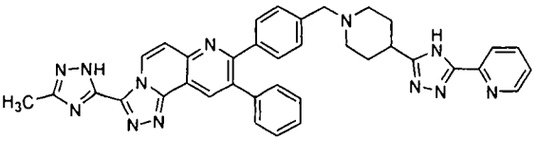
A una solución agitada de **9-2** (5 g, 8,9 mMol) en 1,4-dioxano anhidro (20 ml) se añadió hidrazina (5,9 ml, 188,1mMol). La solución se calentó a 100°C en un reactor de microondas durante 5 minutos. El disolvente se retiró *a vacío* y se secó azeotrópicamente con tolueno tres veces. El sólido en bruto se trituró con una solución de $NaHCO_3$ saturada durante 20 minutos. La suspensión se filtró y se lavó con cantidades copiosas de agua. El sólido se secó azeotrópicamente con tolueno tres veces proporcionando **9-3** como un sólido canela. CL/EM (M+1) calculado: 554,6; observado: 554,2.

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**9-4**)

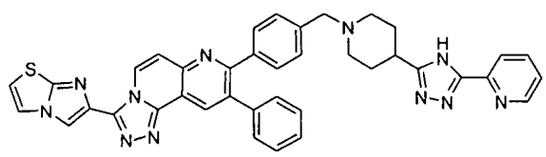
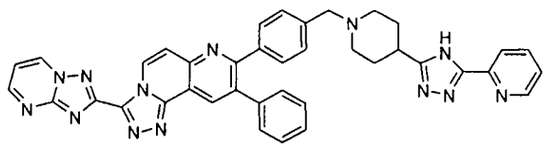
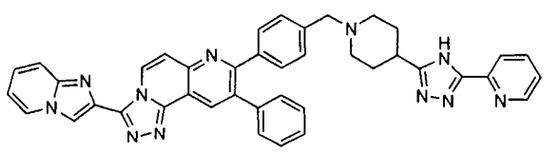
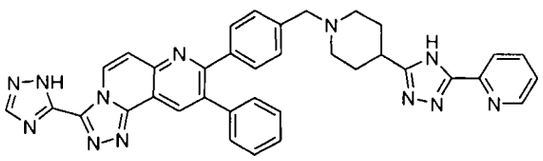
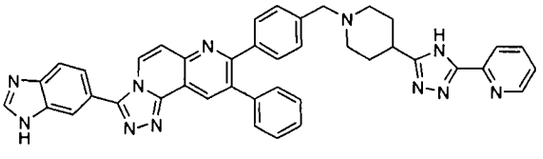
A una solución agitada de **9-3** (2,0 g, 3,6 mMol), HOBT (0,5 g, 3,9 mMol), y ácido 1H-1,2,3-triazol-4-carboxílico (0,4g, 3,9 mMol) en DMF anhidro (20 ml) se añadió DIEA (1,2 ml, 7,2 mMol) seguido por EDC (0,76 g, 3,9 mMol). La solución se agitó a temperatura ambiente durante toda una noche. La solución se trató con 2 ml de ácido acético y se calentó a 80°C durante 3 horas. Tras enfriar a temperatura ambiente, la solución se filtró a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **9-4** como un sólido. Masa (M+1) calculada: 631,2789 observada: 631,2778.

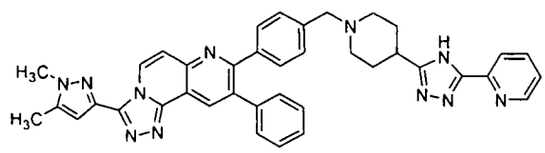
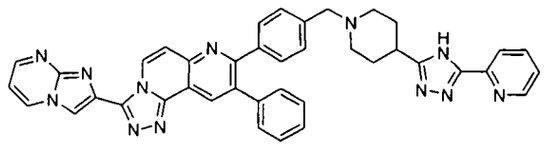
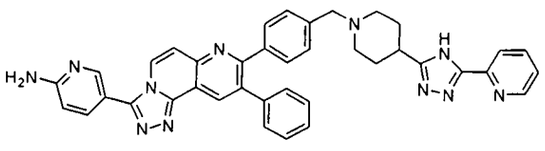
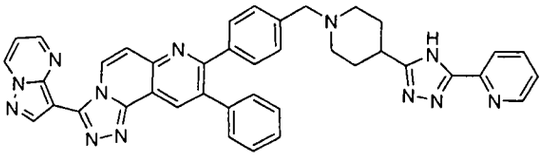
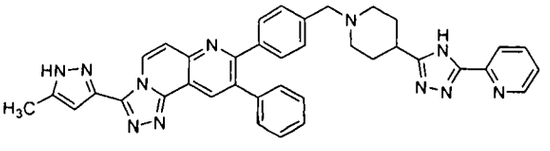
La siguiente tabla (Tabla 3) contiene compuestos fabricados usando los procedimientos de Esquema 9, sustituyendo la amina apropiada por **8-9** y el ácido carboxílico apropiado por ácido 1H-1,2,3-triazol-4-carboxílico. Se aislaron compuestos **9-5** – **9-8** y **9-13** – **9-25** como sales de HCl. Se aislaron compuestos **9-9** – **9-12** como sales de TFA.

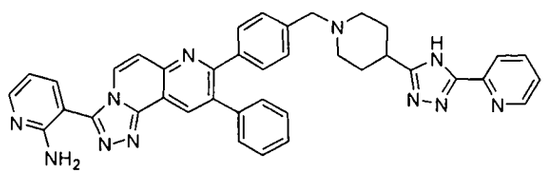
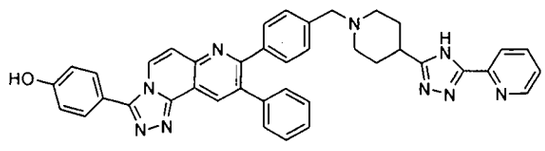
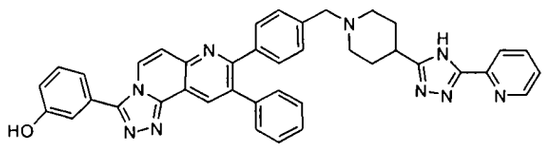
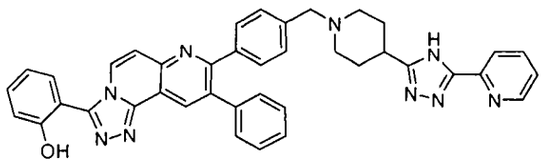
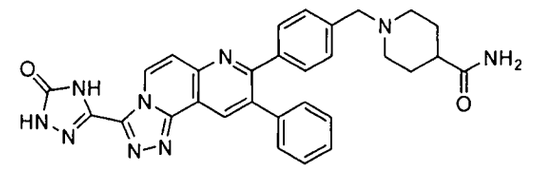
Tabla 3

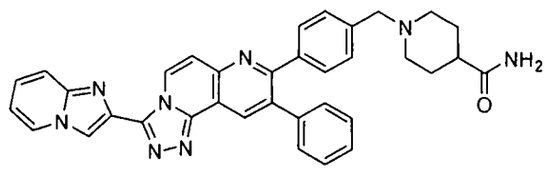
| Cmp | Estructura | Nombre | LREM m/z (M+H) |
|---|---|---|---|
| 9-5 |  | 3-(1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina | 630,2831 |
| 9-6 |  | [9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-il]metilcarbamato de *terc*-butilo | 693,3394 |
| 9-7 |  | [9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol | 594,2703 |
| 9-8 |  | 5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]-2,4-dihidro-3H-1,2,4-triazol-3-ona | 647,2729 |
| 9-9 |  | 3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4- | 645,2948 |

230

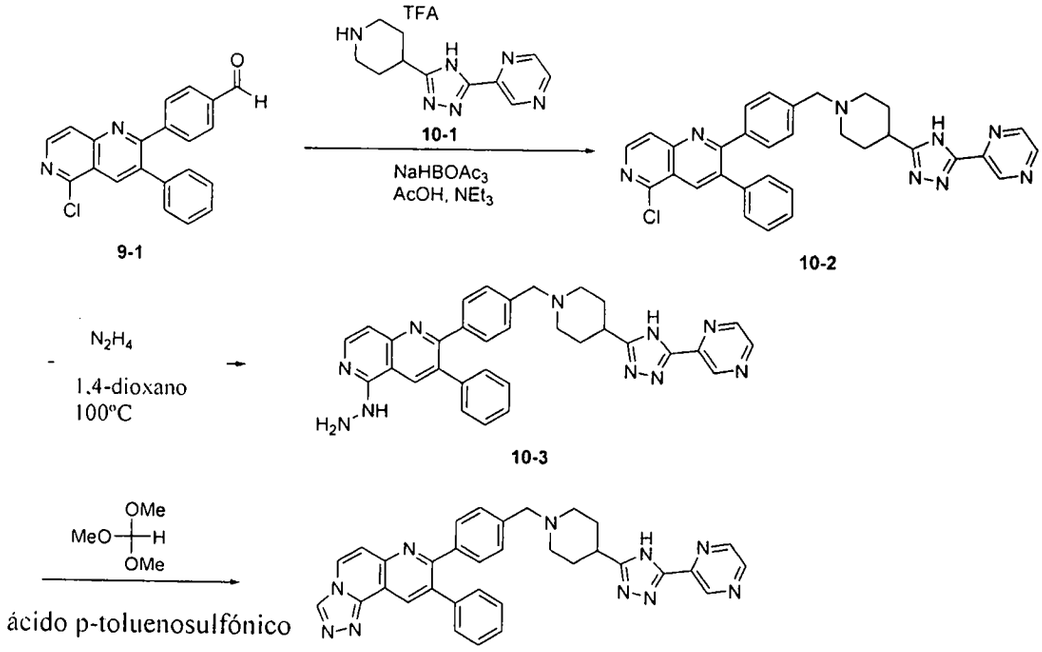
| | | | |
|---|---|---|---|
| | | f]-1,6-naftiridina | |
| 9-10 |  | 3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 686,2547 |
| 9-11 |  | 9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 682,2902 |
| 9-12 |  | 3-imidazo[1,2-a]piridin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | LREM (M+1)= 680,3 |
| 9-13 |  | 9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 631,2792 |
| 9-14 |  | 3-(1H-benzimidazol-6-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1- | 680,2988 |

| | | | |
|---|---|---|---|
| | | il]metil} fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina | |
| 9-15 |  | 3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 658,3145 |
| 9-16 |  | 3-imidazo[1,2-a]pirimidin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 681,2949 |
| 9-17 |  | 5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina | 656,2988 |
| 9-18 |  | 9-fenil-3-pirazolo[1,5-a]pirimidin-3-il-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 681,2951 |
| 9-19 |  | 3-(5-metil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 644,2998 |

| | | | |
|---|---|---|---|
| 9-20 |  | 3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piperidin-2-amina | 656,298 |
| 9-21 |  | 4-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol | 656,288 |
| 9-22 |  | 3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol | 656,288 |
| 9-23 |  | 2-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol | 656,2894 |
| 9-24 |  | 1-{4-[3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida | 546,2344 |

| | | | |
|---|---|---|---|
| 9-25 |  | 1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]piperidina-4-carboxamida | 579,2598 |

ESQUEMA 10




9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**10-4**)

2-(3-piperidin-4-il-1*H*-1,2,4-triazol-5-il)pirazina (**10-1**)

A una solución de ácido 1-(*terc*-butoxicarbonil)piperidina-4-carboxílico (120 g, 520 mmol) en DCM (250 ml) se añadió carbonildiimidazol (96 g, 590 mmol) en partes a temperatura ambiente. Después de 30 minutos, se añadió la mezcla de reacción a una solución recientemente preparada de hidrazina (27 g, 840 mmol) en DCM (100 ml). Después de 30 minutos, se lavó la reacción con una solución saturada de carbonato de sodio, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. El sólido resultante se suspendió en éter y se filtró dando 4-(hidrazinocarbonil)piperidina-1-carboxilato de *terc*-butilo como un sólido blanco. RMN $^1$H (400 MHz, DMSO-$d_6$): δ 9,00 (s, 1H), 4,15-

4,10 (s, 2H), 3,95-3,90 (m, 2H), 2,80-2,60 (m, 2H), 2,25-2,20 (m, 1H), 1,62-1,55 (m, 2H), 1,40 (s, 9H).

Se trató una solución de pirazinacarbonitrilo (2,0 g, 19 mmol) en metanol (20 ml) con metóxido de sodio en metanol (25% en peso, 1,3 ml, 5,7 mmol) a temperatura ambiente. Después de 30 minutos, se añadió una solución de 4-(hidrazinocarbonil)piperidina-1-carboxilato de *terc*-butilo (4,6 g, 19 mmol) en metanol (20 ml) y la reacción se calentó a reflujo durante 19 horas. La mezcla de reacción se concentró, se disolvió en etoxietanol (50 ml) y se calentó a reflujo durante 22 horas. La reacción se enfrió a temperatura ambiente, se desactivó con ácido acético (0,38 ml, 6,6 mmol) y se concentró. El residuo se suspendió en éter y se filtró dando 4-(5-pirazin-2-il-1*H*-1,2,4-triazol-3-il)piperidina-1-carboxilato de *terc*-butilo como un sólido. HREM ($M+H^+$): observado = 331,1876, calculado = 331,1877; RMN $^1H$ (400 MHz, $CD_3OD$): δ 9,29 (d, J = 1,6 Hz, 1H), 8,70 (dd, J = 2,4, 1,6 Hz, 1H), 8,64 (d, J = 2,4 Hz, 2H), 4,19-4,15 (m, 2H), 3,15-3,09 (m, 1H), 2,97 (m, 2H), 2,07-2,03 (m, 2H), 1,84-1,75 (m, 2H), 1,48 (s, 9H).

Se agitó una solución de4-(5-pirazin-2-il-1*H*-1,2,4-triazol-3-il)piperidina-1-carboxilato de *terc*-butilo (6,0 g, 18 mmol) en ácido trifluoroacético (25 ml) a temperatura ambiente. Después de 1 hora, se concentró la reacción. El sólido resultante se suspendió en acetato de etilo y metanol y se filtró dando **10-1** como la sal de TFA. La sal se disolvió en acetonitrilo:agua 1:1, se cargó sobre una resina de intercambio iónico SCX, se aclaró con acetonitrilo, y se eluyó con NH3 al 10% en etanol dando **10-1** como un sólido. RMN $^1H$ (400 MHz, $CDCl_3$): δ 9,28-9,26 (m, 1H), 8,70-8,68 (m, 1H), 8,60-8,58 (m, 1H), 3,35-3,22 (m, 2H), 3,15-3,05 (m, 1H), 2,90-2,85 (m, 2H), 2,15-2,08 (m, 2H), 1,95-1,90 (m, 2H).

5-cloro-3-fenil-2-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**10-2**)

A una solución agitada de **9-1** (1 g, 2,9 mMol) y **10-1** (1,09 g, 3,2 mMol) en NMP (10 ml) se añadió trietilamina (0,8 ml, 5,8 mMol) seguida por ácido acético (0,3 ml, 5,8 mMol). Después de agitar a temperatura ambiente durante toda una noche, se añadió triacetoxiborohidruro de sodio (0,6 g, 2,9 mMol) por partes. Tras completación, la reacción se diluyó con acetato de etilo y se lavó con $NaHCO_3$ saturado, seguido por agua, después salmuera. La fase orgánica se secó con $Na_2SO_4$ y $MgSO_4$, se filtró y se concentró *a vacío*. El residuo en bruto se purificó usando cromatografía ultrarrápida en sílice (gradiente: MeOH al 0%-MeOH al 10% en $CHCl_3$ durante 25 minutos) proporcionando **10-2** como un sólido. CL/EM (M+1) calculado: 560,1; observado: 560,2

5-hidrazino-3-fenil-2-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**10-3**)

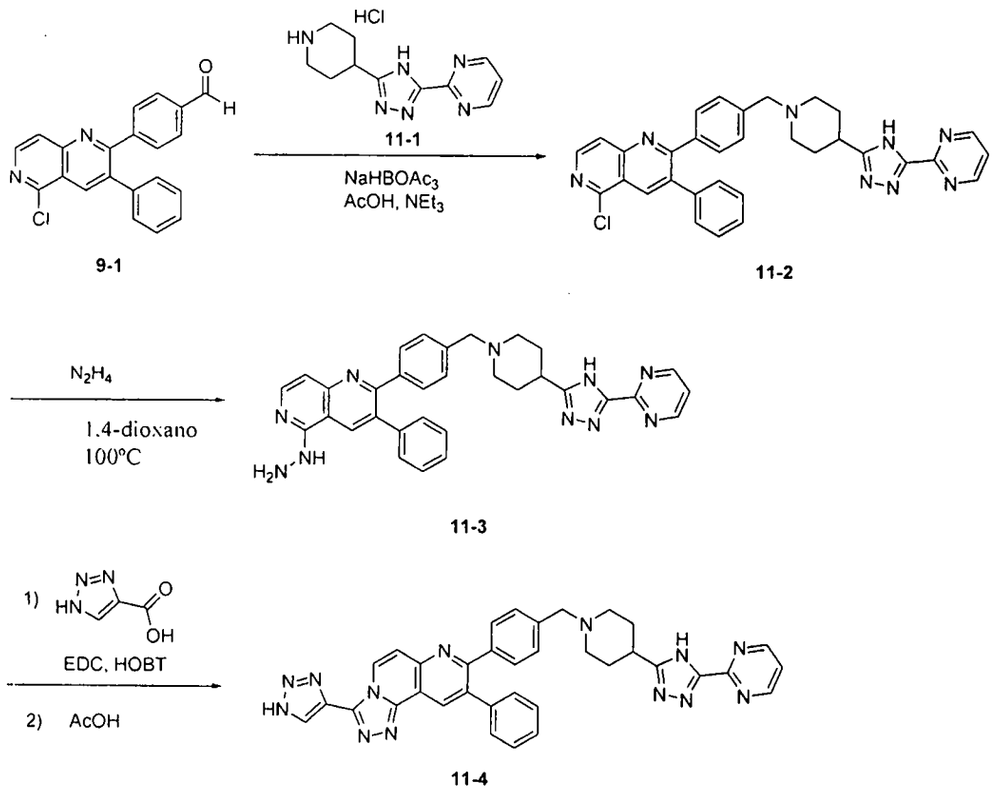
A una solución agitada de **10-2** (0,5 g, 0,9 mMol) en 1,4-dioxano anhidro (5 ml) se añadió hidrazina (0,56 ml, 17,8 mMol). La solución se calentó a 100°C en un reactor de microondas durante 20 minutos. El disolvente se retiró *a vacío* y se secó azeotrópicamente con tolueno tres veces. El sólido en bruto se trituró con una solución de $NaHCO_3$ saturada durante 20 minutos. La suspensión se filtró y se lavó con cantidades copiosas de agua. El sólido se

secó azeotrópicamente con tolueno tres veces proporcionando **10-3** como un sólido canela. CL/EM (M+1) calculado: 555,6; observado: 555,2

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**10-4**)

A una solución agitada de **10-3** (0,5 g, 0,9 mMol) en 16 ml de tolueno:metanol 3:1 se añadió ortoformiato de trimetilo (0,3 g, 2,7 mMol) y monohidrato de ácido *p*-toluenosulfónico (0,017 g, 0,09 mMol). La reacción se calentó a 100°C en un reactor de microondas durante 1 hora. Después de enfriar a temperatura ambiente, se eliminó el disolvente bajo presión reducida. El producto se purificó en una HPLC en fase reversa de C18 dando **10-4** como un sólido. Masa (M+1) calculada: 565,2571 observada: 565,2523

ESQUEMA 11




9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**11-4**)

2-(3-piperidin-4-il-1*H*-1,2,4-triazol-5-il)pirimidina (**11-1**)

Una mezcla de 4-(hidrazinocarbonil)piperidina-1-carboxilato de *terc*-butilo (10,1 g, 41,5 mmol) y 2-cianopirimidina (4,36 g, 41,5 mmol) en 1-butanol (20 ml) se calentó a reflujo durante 48 horas. El residuo se concentró, se suspendió en éter y se filtró dando 4-(5-pirimidin-2-il-1*H*-1,2,4-triazol-3-il)piperidina-1-carboxilato de *terc*-butilo como un sólido. EM

($M+H^+$): 331,2 observado; RMN-$^1$H (400 MHz, $CD_3OD$): δ 8,92 (d, J=4,0Hz, 2H), 7,52 (t, J=4,0 Hz, 1H), 4,18-4,15 (m, 2H), 3,14-3,08 (m, 1H), 2,98 (s.a, 2H), 2,07-2,01 (m, 2H), 1,85-1,77 (m, 2H), 1,48 (s, 9H).

A una solución de 4-(5-pirimidin-2-il-1*H*-1,2,4-triazol-3-il)piperidina-1-carboxilato de *terc*-butilo (13,6 g, 41,1 mmol) en metanol (30 ml) y DCM (15 ml) se añadió una solución saturada de HCl en acetato de etilo (60 ml). Después de 2 horas, se concentró la reacción. El sólido resultante se suspendió en acetato de etilo y metanol y se filtró dando **11-1** como la sal de HCl. La sal se disolvió en acetonitrilo:agua 1:1, se cargó sobre una resina de intercambio iónico SCX, se aclaró con acetonitrilo, y se eluyó con $NH_3$ al 10% en etanol dando **11-1** como un sólido. EM ($M+H^+$): 231,2

5-cloro-3-fenil-2-(4-{[4-(5-pirimidin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**11-2**)

A una solución agitada de **9-1** (0,25 g, 0,73 mMol) y **11-1** (0,23 g, 0,87 mMol) en NMP (5 ml) se añadió trietilamina (0,3 ml, 2,2 mMol) seguida por ácido acético (0,082 ml, 1,5 mMol). Después de agitar a temperatura ambiente durante toda una noche, se añadió triacetoxiborohidruro de sodio (0,18 g, 0,87 mMol). Tras completación, la reacción se diluyó con acetato de etilo y se lavó con $NaHCO_3$ saturado, seguido por agua, después salmuera. La fase orgánica se secó con $Na_2SO_4$ y $MgSO_4$, se filtró y se concentró *a vacío* proporcionando **11-2**. CL/EM (M+1) calculado: 559,1; observado: 559,3

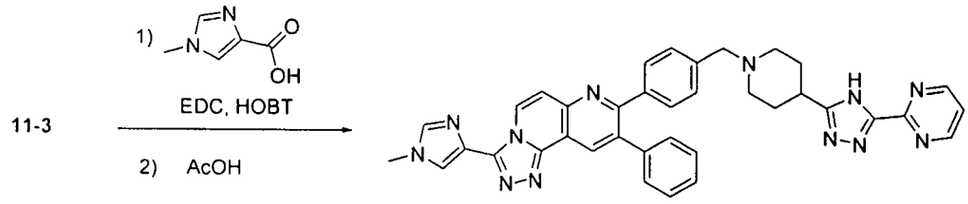
5-hidrazino-3-fenil-2-(4-{[4-(5-pirimidin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**11-3**)

A una solución agitada de **11-2** (0,4 g, 0,7 mMol) en 1,4-dioxano anhidro (3 ml) se añadió hidrazina (0,45 ml, 14,5 mMol). La solución se calentó a 100°C en un reactor de microondas durante 5 minutos. El disolvente se retiró *a vacío* y se secó azeotrópicamente con tolueno tres veces proporcionando **11-3**. CL/EM (M+1) calculado: 555,6; observado: 555,4

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**11-4**)

A una solución agitada de **11-3** (0,2 g, 0,36 mMol), HOBT (0,05 g, 0,4 mMol), y ácido 1H-1,2,3-triazol-4-carboxílico (0,05 g, 0,4 mMol) en DMF anhidro (2 mL) se añadió DIEA (0,18 ml, 1,1 mMol) seguido por EDC (0,08 g, 0,4 mMol). La solución se calentó en el reactor de microondas durante 30 minutos a 80°C. La solución se trató después con 0,5 ml de ácido acético y se calentó a 80°C en el reactor de microondas durante 10 minutos. Tras enfriar a temperatura ambiente, la solución se hizo pasar a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **11-4** como un sólido. Masa (M+1) calculada: 632,2742 observada: 632,274

ESQUEMA 12

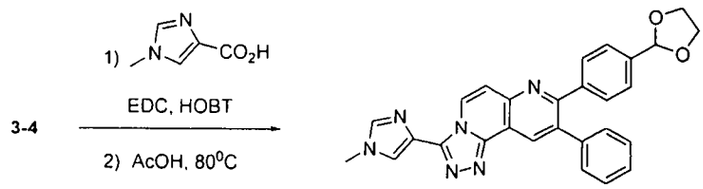



12-1

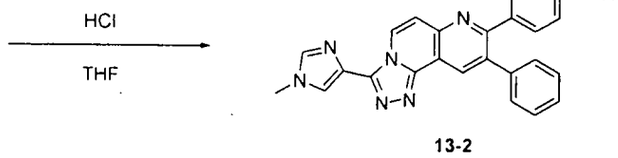
3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirimidin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**12-1**)

A una solución exagerada de **11-3** (0,23 g, 0,4 mMol), HOBT (0,06 g, 0,45 mMol), y ácido 1-metil-1H-imidazol-4-carboxílico (0,06 g, 0,45 mMol) en DMF anhidro (2 ml) se añadió DIEA (0,13 ml, 0,8 mMol) seguido por EDC (0,09 g, 0,5 mMol). La solución se calentó en el reactor de microondas durante 15 minutos a 80°C. La solución se trató después con 0,2 ml de ácido acético y se calentó a 80°C en el reactor de microondas durante 20 minutos. Tras enfriar a temperatura ambiente, la solución se hizo pasar a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **12-1** como un sólido. Masa (M+1) calculada: 632,2742 observada: 632,274

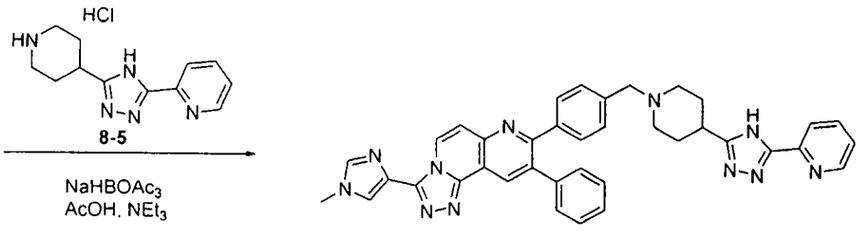
ESQUEMA 13




13-1




13-2




13-3

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-3**)

8-[4-(1,3-dioxolan-2-il)fenil]-3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-1**)

A una solución agitada de **3-4** (5 g, 13 mMol), HOBT (1,9 g, 14,3 mMol), y ácido 1-metil-1H-imidazol-4-carboxílico (2 g, 15,6 mMol) en DMF anhidro (100 ml) se añadió EDC (2,7 g, 14,3 mMol). La solución se agitó durante toda una noche a temperatura ambiente . La solución se trató después con 24 ml de ácido acético y se calentó a 80°C en un baño de aceite durante 5 horas. Tras enfriar a temperatura ambiente, se añadió un volumen igual de agua y la suspensión resultante se filtró y se lavó con cantidades copiosas de agua. El sólido recogido se secó azeotrópicamente con tolueno tres veces proporcionando **13-1** como un sólido canela. Masa (M+1) calculada: 475,1877 observada: 475,1871.

4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]benzaldehído (**13-2**)

A una solución de **13-1** (2 g, 4,2 mMol) en THF (32 ml) se añadió HCl 1N (32 ml). Una suspensión desarrollada como la reacción se agitó a temperatura ambiente durante 1 hora. La reacción se desactivó después con 100 ml de una solución saturada de $NaHCO_3$. La suspensión se filtró y se lavó con agua. El sólido recogido se secó azeotrópicamente con tolueno tres veces proporcionando **13-2** como un sólido canela. Masa (M+1) calculada: 431,1615 observada: 431,1616.

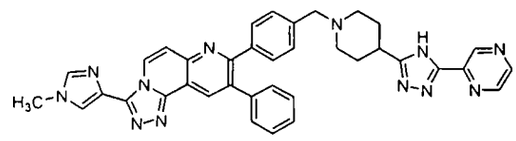
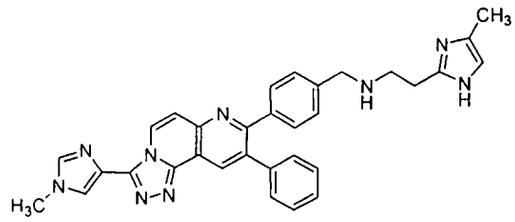
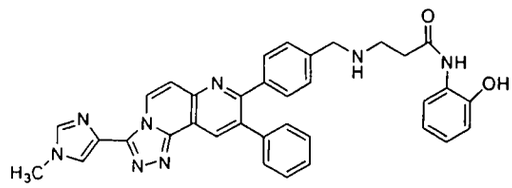
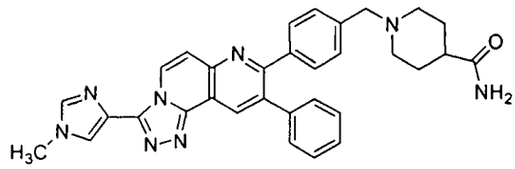
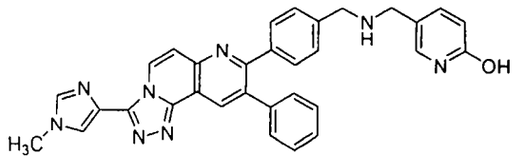
3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-3**)

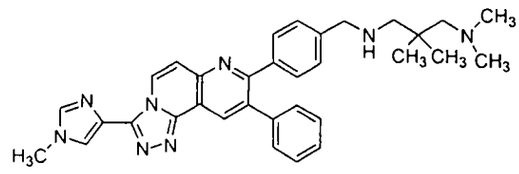
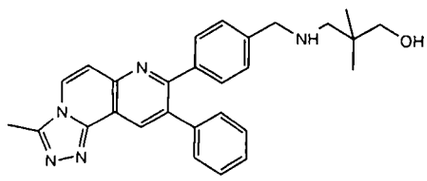
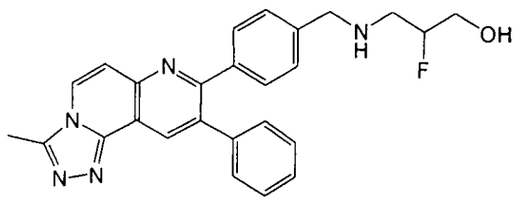
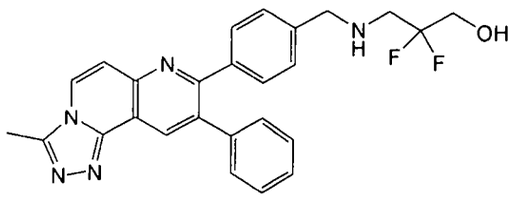
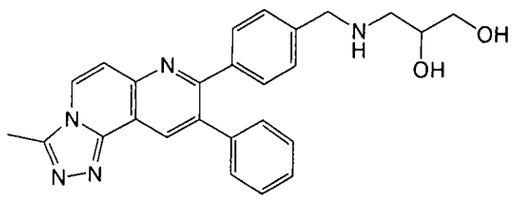
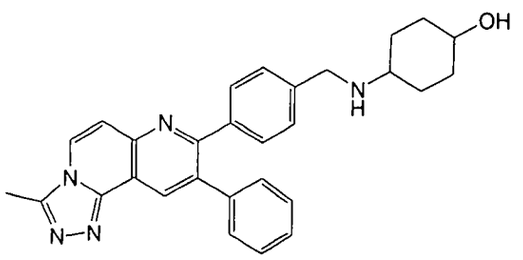
A una solución agitada de **13-2** (0,5 g, 1,2 mMol) y **8-5** (0,34 g, 1,3 mMol) en NMP (10 ml) se añadió trietilamina (0,33 ml, 2,3 mMol) seguida por ácido acético (0,13 ml, 2,3 mMol). Después de agitar durante toda una noche a temperatura ambiente, se añadió triacetoxiborohidruro de sodio (0,3 g, 1,3 mMol) por partes. Después de agitar durante 6 horas, la solución se filtró a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **13-3** como un sólido. Masa (M+1) calculada: 644,2993 observada: 644,2988

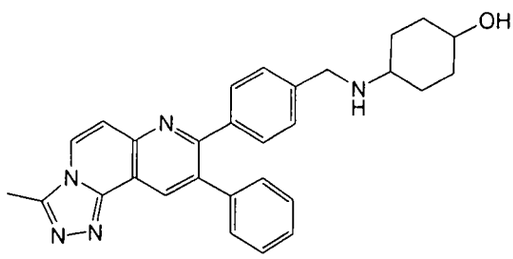
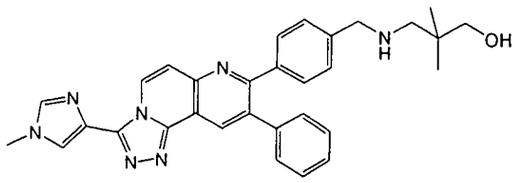
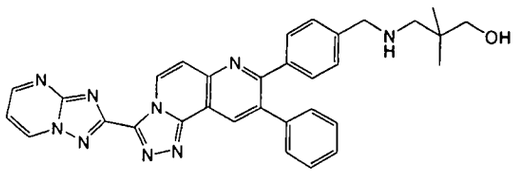
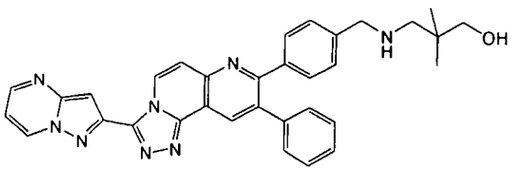
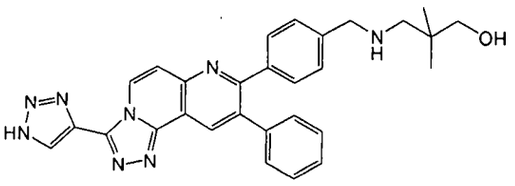
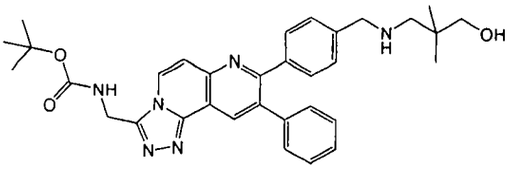
La siguiente tabla (Tabla 4) contiene compuestos fabricados usando los procedimientos de Esquema 13, sustituyendo la amina apropiada por **8-5**. Se aislaron compuestos **13-4** – **13-7**, **13-10** – **13-19** y **13-21** como la sal de HCl. Se aislaron compuestos **13-8** y **13-9** como sales de TFA.

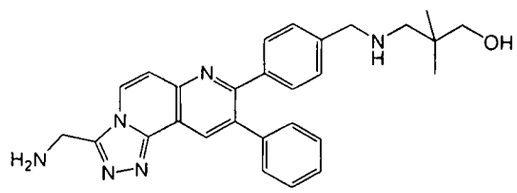
240

Tabla 4

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| 13-4 |  | 3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenii)[1,2,4]triazolo[3,4-f]-1,6-naftiridina | 645,2946 |
| 13-5 |  | N-[2-(4-metil-1H-imidazol-2-il)etil]-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}amina | 540,2609 |
| 13-6 |  | $N^1$-(2-hidroxifenil)-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-beta-alaninamida | 595,2564 |
| 13-7 |  | 1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida | 543,2611 |
| 13-8 |  | 5-[({4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}amino)metil]piridin-2-ol | 539,2302 |

| | | | |
|---|---|---|---|
| 13-9 |  | $N^1$,$N^1$,2,2-tetrametil-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] bencil}propano-1,3-diamina | 545,3125 |
| 13-10 |  | 3-hidroxi-2,2-dimetil-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 452,2659 Observ.: 452,2655 |
| 13-11 |  | 2-fluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 442,2038 Observ.: 442,2021 |
| 13-12 |  | 2-fluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 460,1944 Observ.: 460,1926 |
| 13-13 |  | 2,3-dihidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 440,2081 Observ.: 440,2076 |
| 13-14 |  | 4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]ciclohexanamina | Calc.: 464,2445 Observ.: 464,2448 |

| | | | |
|---|---|---|---|
| 13-15 |  | 4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]ciclohexanamina | Calc.: 464,2445 Observ.: 464,2438 |
| 13-16 |  | 3-hidroxi-2,2-dimetil-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}propan-1-amina | Calc.: 518,2663 Observ.: 518,2663 |
| 13-17 |  | 3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 556,2568 Observ.: 556,2570 |
| 13-18 |  | 3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 555,2616 Observ.: 555,2575 |
| 13-19 |  | 3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina | Calc.: 505,2459 Observ.: 505,2453 |
| 13-20 |  | {[8-(4-{[(3-hidroxi-2,2-dimetilpropil)amino]metil}fenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metil}carbamato de | Calc.: 567,3018 Observ.: 567,3015 |

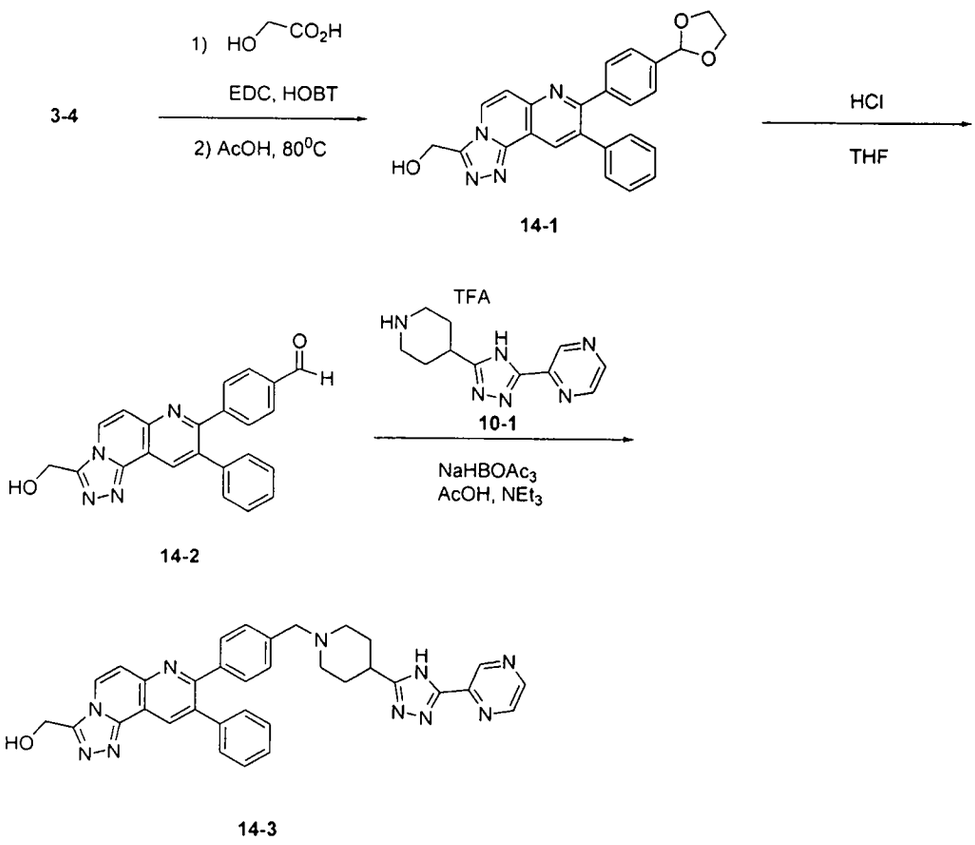
| | | | |
|---|---|---|---|
| | | *terc*-butilo | |
| **13-21** |  | N-{4-[3-(amoniometil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-3-hidroxi-2,2-dimetilpropan-1-amina | Calc.: 467,2554 Observ.: 467,2553 |

Compuesto **13-4**

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**13-4**)

A una solución agitada de **13-2** (1,5 g, 3,5 mMol) y **10-1** (1,4 g, 4,0 mMol) en NMP (30 ml) se añadió trietilamina (1 ml, 7 mMol) seguida por ácido acético (0,4 ml, 7 mMol). Después de agitar durante toda una noche a temperatura ambiente, se añadió triacetoxiborohidruro de sodio (0,9 g, 4,2 mMol) por partes. Después de agitar durante 6 horas, la solución de $NaHCO_3$ saturada se añadió hasta que el pH estuvo por encima de 7. La suspensión resultante se filtró y se lavó con agua. El sólido se secó azeotrópicamente con tolueno tres veces y se purificó usando cromatografía ultrarrápida en fase normal (gradiente: $CHCl_3$ al 100%-MeOH al 10% en $CHCl_3$ durante 40 minutos) proporcionando **13-4** como un sólido blanco. Masa (M+1) calculada: 645,2946 observada: 645,2946

ESQUEMA 14




[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**14-3**)

{8-[4-(1,3-dioxolan-2-il)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol (**14-1**)

A una solución agitada de **3-4** (5 g, 13 mMol), HOBT (1,9 g, 14,3 mMol), y ácido glicólico (1,2 g, 15,6 mMol) en DMF anhidro (100 ml) se añadió EDC (2,7 g, 14,3 mMol). La solución se agitó durante toda una noche a temperatura ambiente . La solución se trató después con 5 ml de ácido acético glacial y se calentó a 80°C en un baño de aceite durante 2 horas. Tras enfriar a temperatura ambiente, la reacción se diluyó con acetato de etilo y se lavó con $NaHCO_{3\,(aq)}$, agua, y salmuera. La fase orgánica se secó con $MgSO_4$, se filtró y se concentró *a vacío* proporcionando **14-1** como un sólido rojo. CL/EM (M+1) calculado: 425,5; observado: 425,6

4-[3-(hidroximetil)-9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il] benzaldehído (**14-2**)

A una suspensión de **14-1** (2,1 g, 4,9 mMol) en THF (50 ml) se añadió HCl 1N (50 ml). Después de agitar a temperatura ambiente durante 30 minutos, la reacción

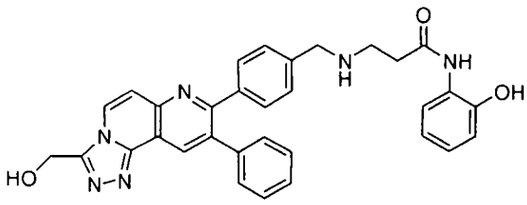
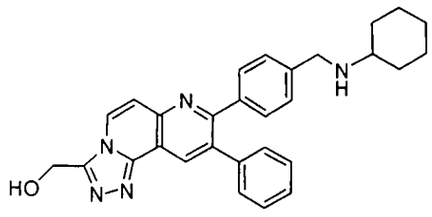
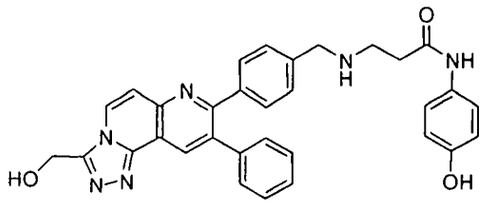
se diluyó con acetato de etilo y se lavó dos veces con agua, seguida por salmuera. La fase orgánica se secó con $MgSO_4$ y $Na_2SO_4$, se filtró y se concentró *a vacío* proporcionando **14-2** como un sólido rojo. Masa (M+1) calculada: 381,1346 observada: 381,1346.

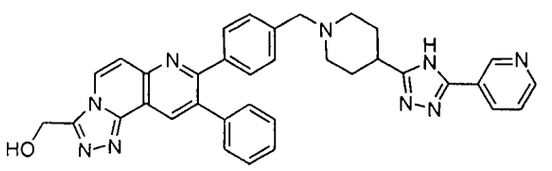
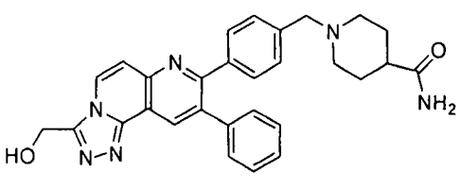
[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol (**14-3**)

A una solución agitada de **14-2** (0,05 g, 0,1 mMol) y **10-1** (0,05 g, 0,15 mMol) en NMP (1 ml) se añadió trietilamina (0,04 ml, 0,26 mMol) seguida por ácido acético (0,01 ml, 0,26 mMol). Después de agitar durante toda una noche a temperatura ambiente, se añadió triacetoxiborohidruro de sodio (0,03 g, 0,2 mMol). Después de agitar durante 6 horas, la solución se filtró a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **14-3** como un sólido. Masa (M+1) calculada: 595,2677 observada: 595,2679

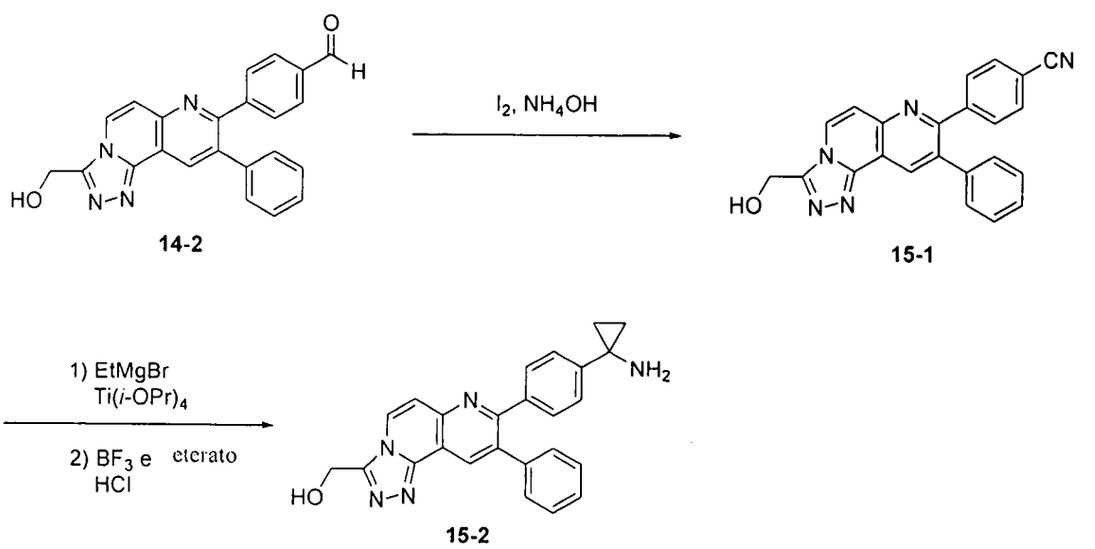
La siguiente tabla (Tabla 5) contiene compuestos fabricados usando los procedimientos de Esquema 14, sustituyendo la amina apropiada por **10-1**. Se aislaron compuestos **14-4**, **14-5**, **14-7** y **14-8** como sales de HCl. Se aisló compuesto **14-6** como una sal de TFA.

Tabla 5

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **14-4** |  | $N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(2-hidroxifenil)-beta-alaninamida | 545,2293 |
| **14-5** |  | (8-{4-[(ciclohexil amino)metil]fenil}-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il)metanol | 464,2435 |
| **14-6** |  | $N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(4-hidroxifenil)-beta-alaninamida | 545,2296 |

| | | | |
|---|---|---|---|
| 14-7 |  | [9-fenil-8-(4-{[4-(5-piridin-3-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol | LREM (M+1)= 594,2 |
| 14-8 |  | 1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida | 493,2344 |

ESQUEMA 15




{8-[4-(1-aminociclopropil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol (**15-2**)

4-[3-(hidroximetil)-9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il] benzonitrilo (**15-1**)

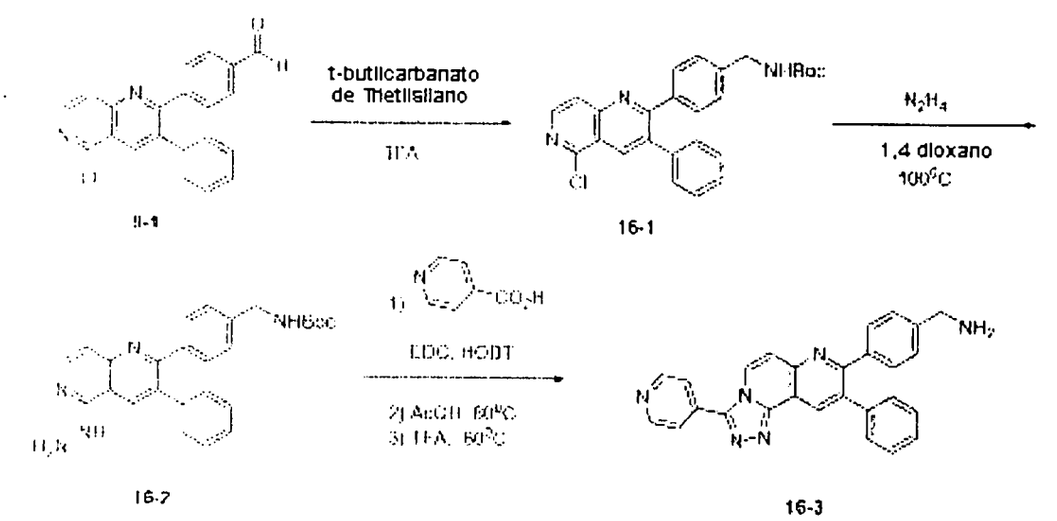
A una suspensión agitada de **14-2** (0,4 g, 1,1 mMol) en THF anhidro (15 ml) se añadieron 3 ml de $NH_4OH$ concentrado. La solución se trató después con yodo (0,4 g, 1,6 mMol) seguido por agitación a temperatura ambiente durante toda una noche. La reacción se desactivó con solución de tiosulfato de sodio saturada (20 ml) y el producto se extrajo en acetato de etilo tres veces. Las fases orgánicas combinadas se lavaron con salmuera, se secaron

con $Na_2SO_4$, se filtraron y se concentraron *a vacío* proporcionando **15-1** como un sólido canela. Masa (M+1) calculada: 378,135 observada: 378,1345

{8-[4-(1-aminociclopropil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol (**15-2**)

Se añadió bromuro de etilmagnesio en éter dietílico (0,4 ml, 1,2 mMol, 3M) a -70°C a una solución de **15-1** (0,1g, 0,3 mmol) e isopropóxido de titanio (IV) (0,17 g, 0,6 mMol) en THF anhidro (7 ml). Después de 10 minutos, el baño frío se eliminó y la reacción se calentó a temperatura ambiente. Después de agitar durante 1 hora, se añadió más bromuro de etilmagnesio en éter dietílico (0,18 ml, 0,5 mMol, 3M) y la reacción se enfrió a 0°C en un baño de hielo y se trató con trifluoruro de boro eterato (0,18 g, 1,2 mMol). La reacción se agitó a 0°C durante 30 minutos después se calentó a temperatura ambiente durante 1 hora. La reacción se desactivó con HCl 1N seguido por agitación durante 3 horas. La solución se basificó con NaOH 1M, se extrajo con cloroformo, se secó con $Na_2SO_4$, se filtró y se concentró *a vacío*. El residuo en bruto se llevó en metanol y se purificó usando una HPLC en fase reversa de C18 dando **15-2** como un sólido. CL/EM (M+1) calculado: 408,4; observado: 408,0

ESQUEMA 16




1-[4-(9-fenil-3-piridin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (**16-3**)

4-(5-cloro-3-fenil-1,6-naftiridin-2-il)benzilcarbamato de *terc*-butilo (**16-1**)

A una solución agitada de **9-1** (7 g, 20,2 mMol) y *t*-butilcarbamato (2,6 g, 22,3 mMol) en acetonitrilo seco (35 ml) se añadió trietilsilano (29,1 ml, 182 mMol) seguido por ácido trifluoroacético (6 ml, 81 mMol). Después de agitar durante 3 horas, la solución se vertió en $NaHCO_3$ y se extrajo en acetato de etilo tres veces. Las fases orgánicas combinadas se lavaron con agua seguida de salmuera. La fase orgánica se secó después con $Na_2SO_4$, se filtró,

y se concentró *a vacío* y se purificó usando cromatografía ultrarrápida en sílice. CL/EM (M+1) calculado: 446,9; observado: 446,1.

4-(5-hidrazino-3-fenil-1,6-naftiridin-2-il)benzilcarbamato de *terc*-butilo (16-2)

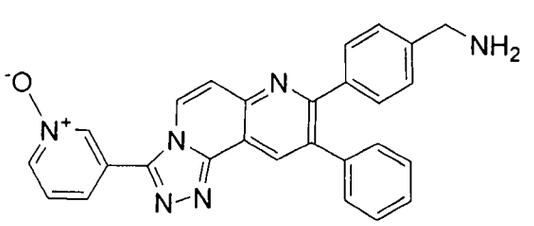
A una solución agitada de **16-1** (6,8 g, 15,2 mMol) en 1,4-dioxano anhidro (20 ml) se añadió hidrazina (10,8 ml, 343 mMol). La solución se calentó a 100°C en un reactor de microondas durante 5 minutos. El disolvente se eliminó *a vacío* y el residuo en bruto se llevó en acetato de etilo y se lavó con solución de $NaHCO_3$ acuosa seguida por salmuera. La fase orgánica se secó con $MgSO_4$, se filtró y se concentró *a vacío* proporcionando **16-2** como un sólido naranja. CL/EM (M+1) calculado: 442,5; observado: 442,2

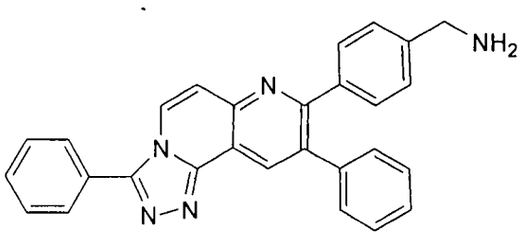
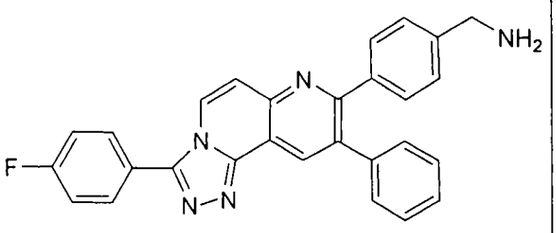
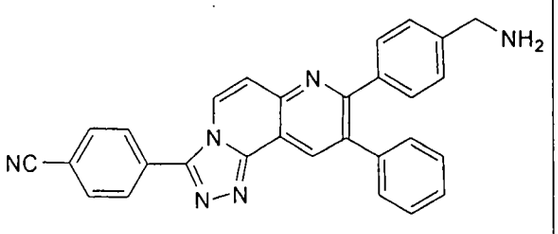
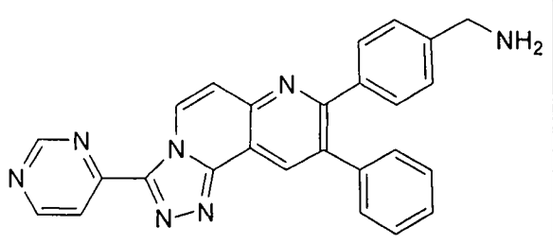
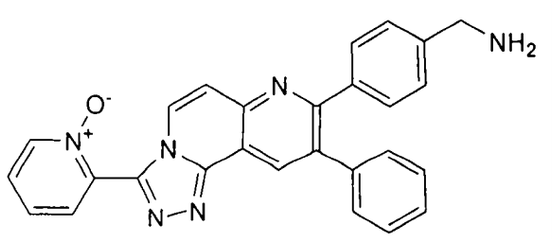
1-[4-(9-fenil-3-piridin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina (16-3)

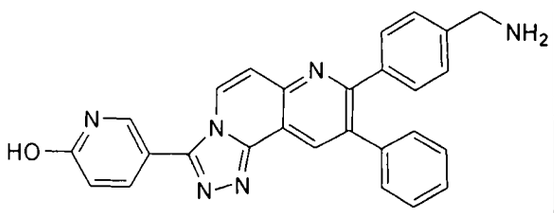
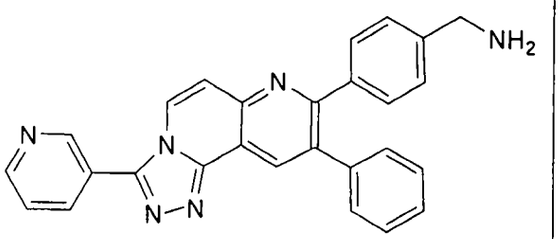
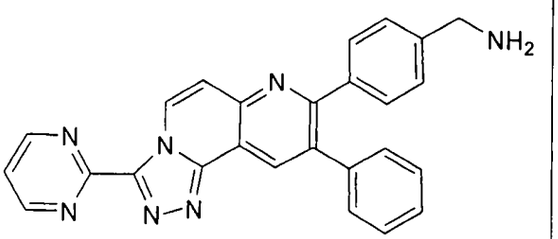
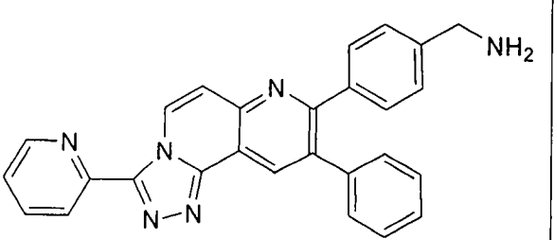
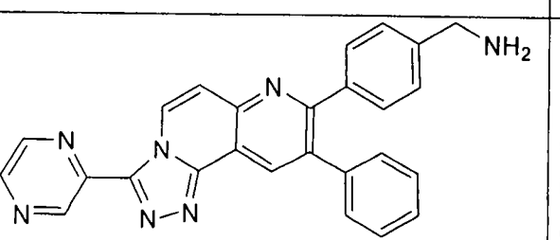
A una solución agitada de **16-2** (0,08 g, 0,2 mMol), HOBT (0,03 g, 0,2 mMol), y ácido isonicotínico (0,02 g, 0,2 mMol) en DMF anhidro (1 ml) se añadió DIEA (0,08 ml, 0,5 mMol) seguido por EDC (0,04 g, 0,2 mMol). La solución se calentó en reactor de microondas a 80°C durante 12 minutos. La solución se trató después con 0,5 ml de ácido acético y se calentó en un reactor de microondas a 80°C durante 30 minutos. Tras enfriar a temperatura ambiente, los productos volátiles se evaporaron a vacío y la solución se filtró a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **16-3** como un sólido. Masa (M+1) calculada: 429,1822 observada: 429,1811

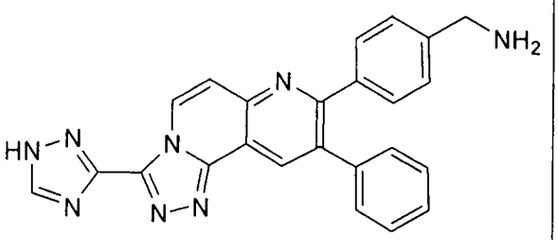
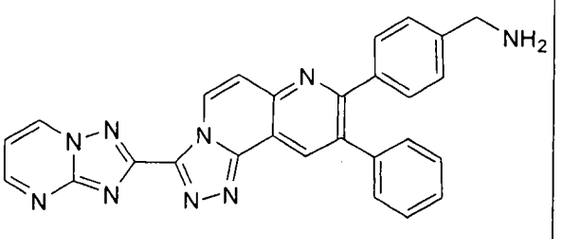
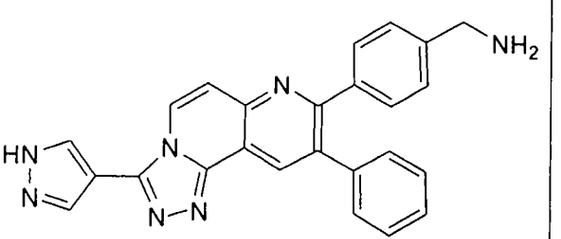
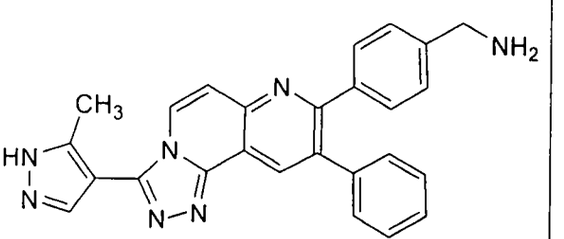
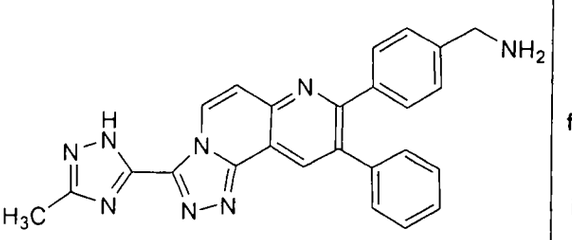
La siguiente tabla (Tabla 6) contiene compuestos fabricados usando los procedimientos para ello del Esquema 16, sustituyendo el ácido carboxílico apropiado por ácido isonicotínico:

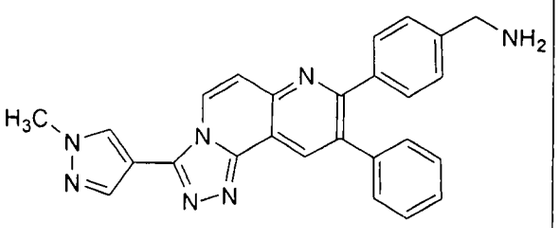
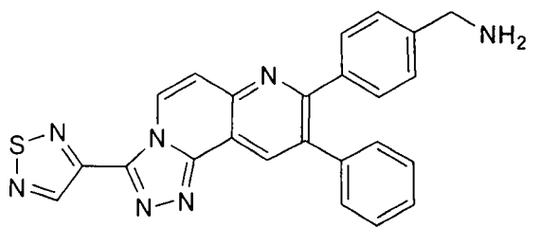
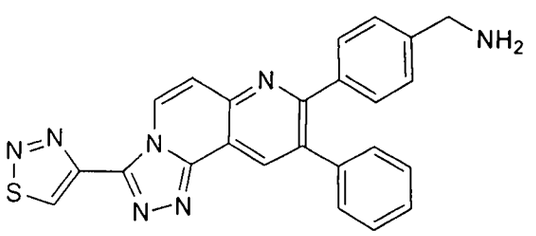
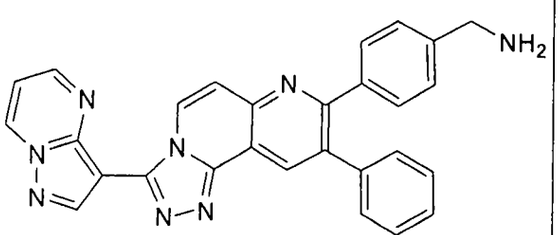
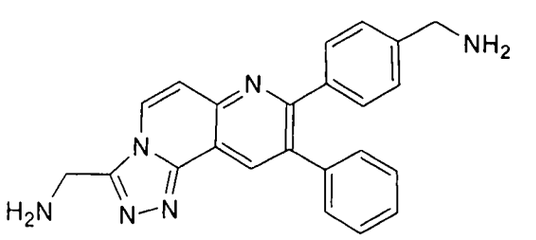
Tabla 6

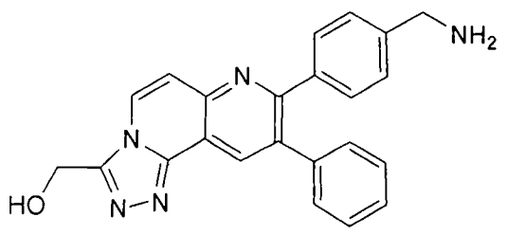
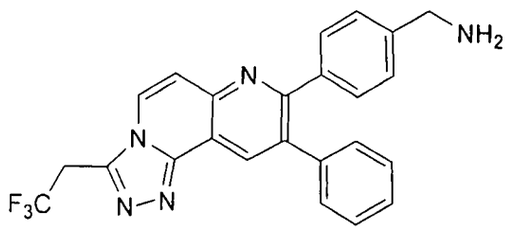
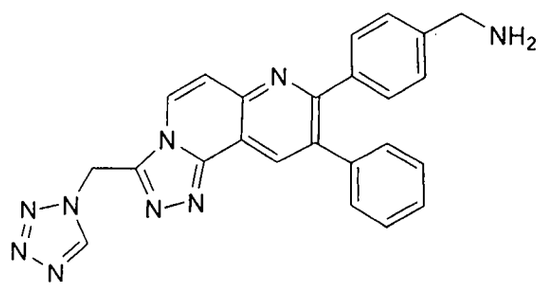
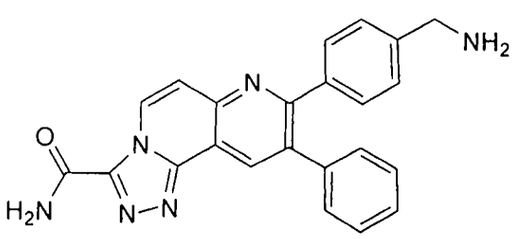
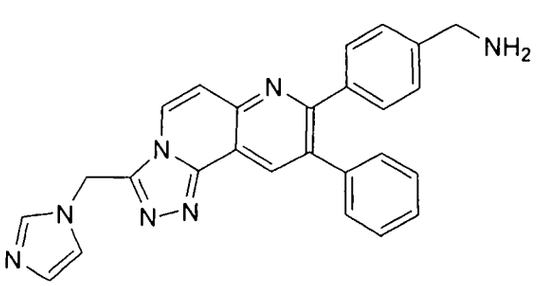
| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **16-4** |  | 1-{4-[3-(1-oxidopiridin-3-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] fenil}metanamina; aislada como la sal de HCl | 445,1772 |

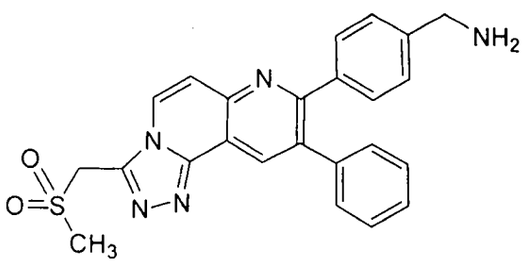
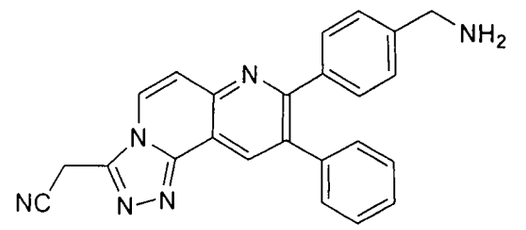
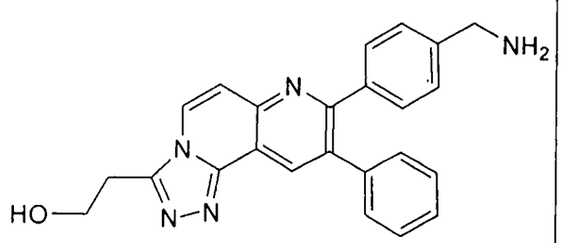
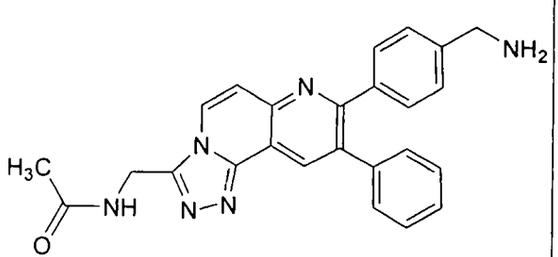
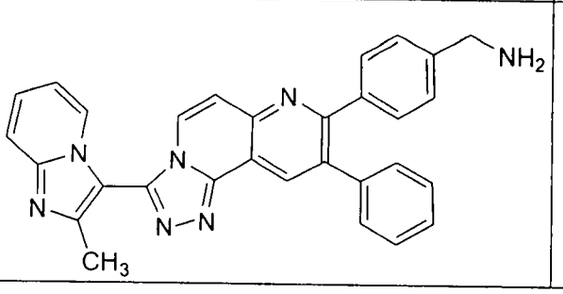
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| 16-5 |  | 1-[4-(3,9-difenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 428,1865 |
| 16-6 |  | 1-{4-[3-(4-fluorofenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 446,177 |
| 16-7 |  | 4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}benzonitrilo; aislado como la sal de HCl | 453,182 |
| 16-8 |  | 4-(9-fenil-3-pirimidin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina; aislada como la sal de HCl | 430,1774 |
| 16-9 |  | 1-{4-[3-(1-oxidopiridin-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 445,174 |

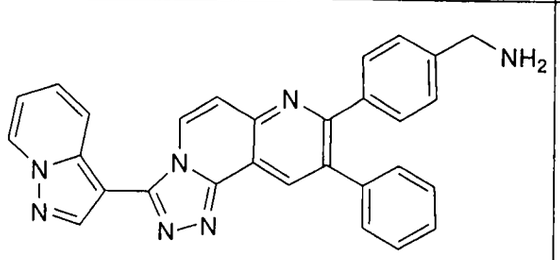
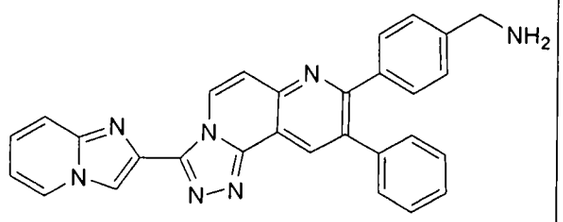
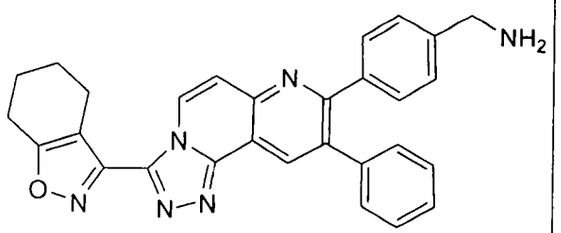
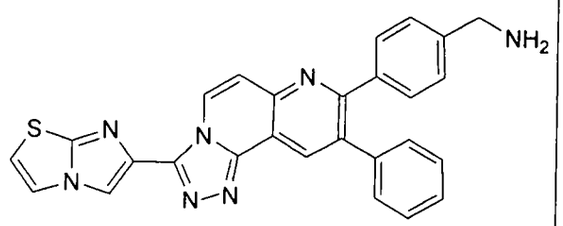
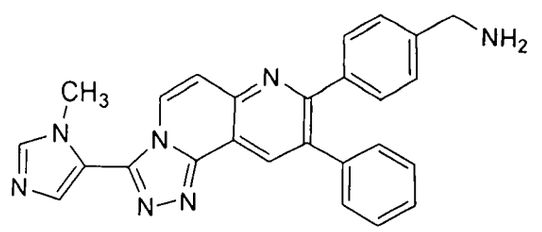
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|---|---|---|---|
| 16-10 |  | 5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}iridina-2-ol; aislado como la sal de HCl | 445,1771 |
| 16-11 |  | 1-[4-(9-fenil-3-piridin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 429,1846 |
| 16-12 |  | 4-(9-fenil-3-pirimidin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina; aislada como la sal de HCl | 430,177 |
| 16-13 |  | 1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamida; aislada como la sal de TFA | LREM (M+1) = 429,1 |
| 16-14 |  | 1-[4-(9-fenil-3-piridin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 430,1775 |

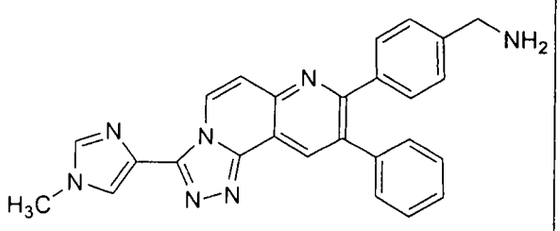
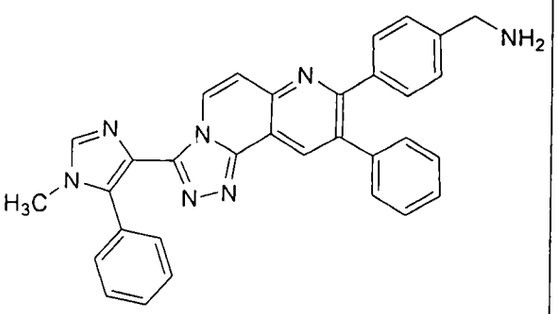
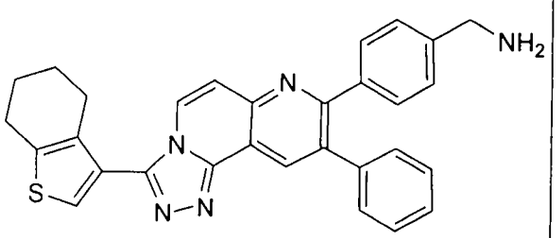
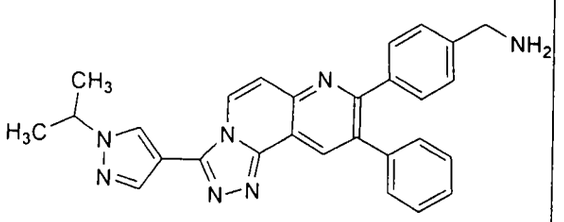
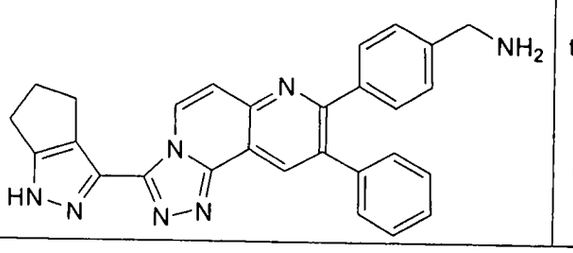
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|---|---|---|---|
| 16-15 |  | 1-{4-[9-fenil-3-(1H-1,2,4-triazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 419,1727 |
| 16-16 |  | 1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 470,1824 |
| 16-17 |  | 1-[4-(9-fenil-3-(1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 418,1764 |
| 16-18 |  | 1-{4-[3-(3-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 432,193 |
| 16-19 |  | 1-{4-[3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 433,182 |

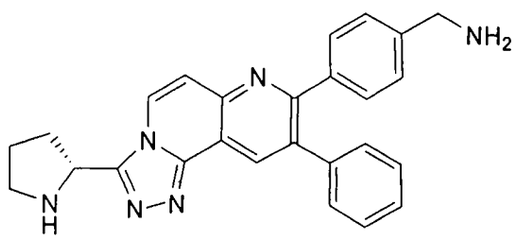
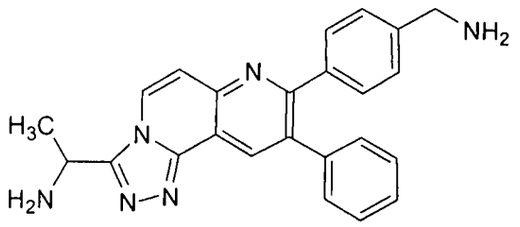
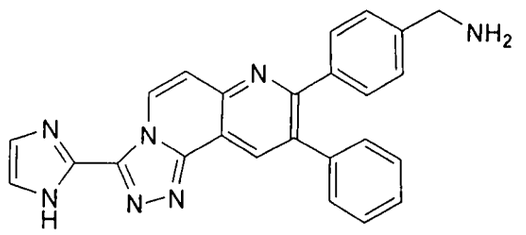
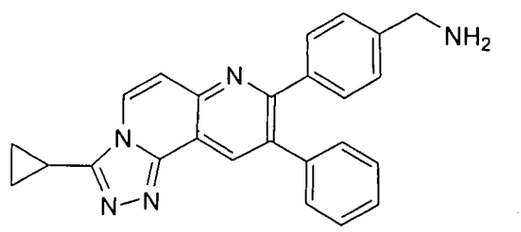
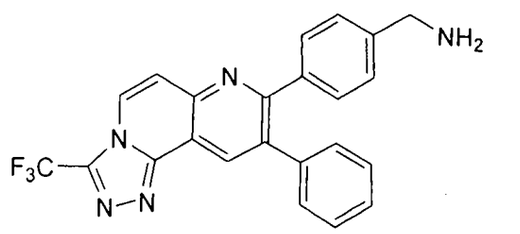
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| 16-20 |  | 1-{4-[3-(1-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 432,193 |
| 16-21 |  | 1-{4-[9-fenil-3-(1,2,5-tiadiazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 436,1341 |
| 16-22 |  | 1-{4-[9-fenil-3-(1,2,3-tiadiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 436,1333 |
| 16-23 |  | 1-{4-[9-fenil-3-pirazolo[1,5-a]pirimidin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 469,1882 |
| 16-24 |  | {8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanamina; aislada como la sal de HCl | 381,1817 |

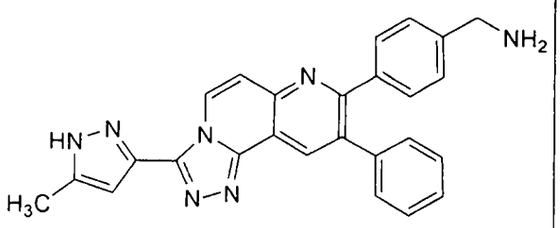
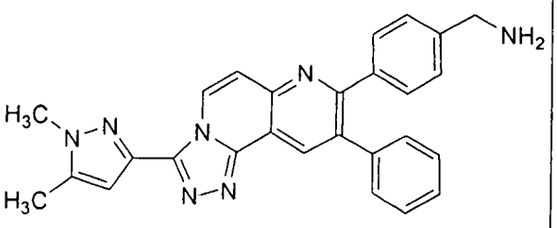
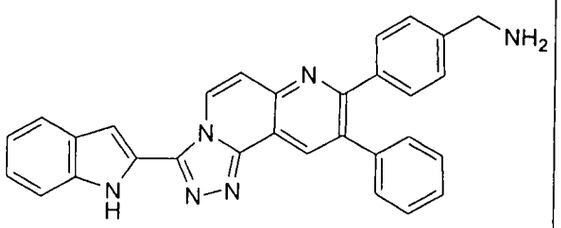
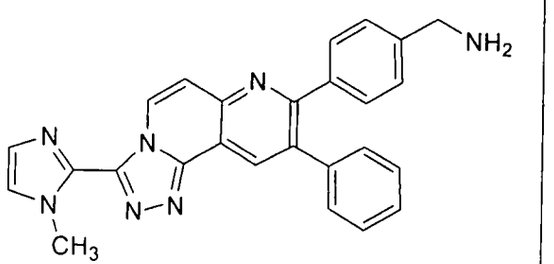
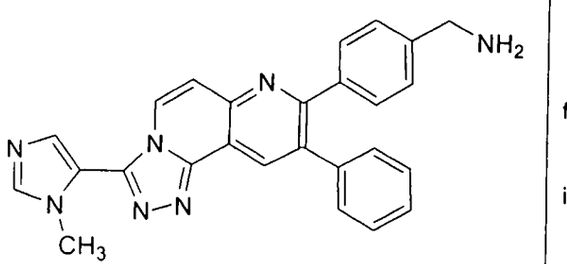
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| 16-25 |  | {8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol; aislado como la sal de HCl | 382,1657 |
| 16-26 |  | 1-{4-[9-fenil-3-(2,2,2-trifluoroetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 434,1584 |
| 16-27 |  | 1-[4-(9-fenil-3-(1H-tetraazol-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 434,1831 |
| 16-28 |  | 8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-carboxamida; aislada como la sal de HCl | LREM (M+1) = 395,2 |
| 16-29 |  | 1-{4-[3-(1H-imidazol-1-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 432,1931 |

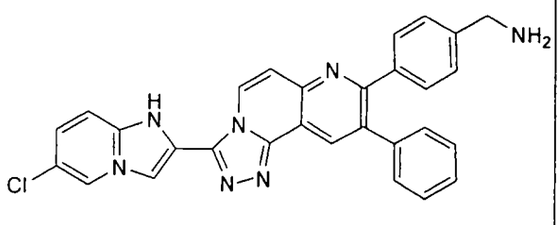
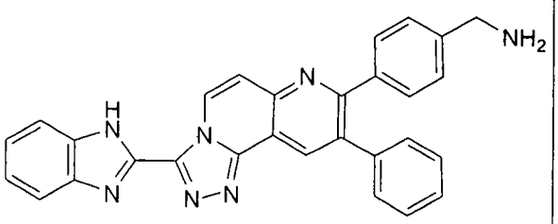
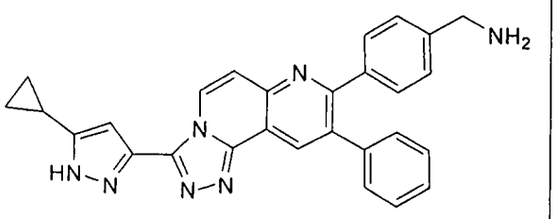
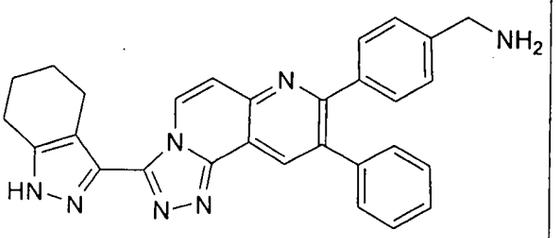
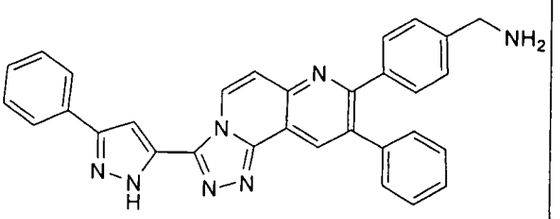
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| 16-30 |  | 1-(4-{3-[(metilsulfonil)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina; aislada como la sal de HCl | 444,1488 |
| 16-31 |  | {8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}acetonitrilo; aislado como la sal de HCl | 391,166 |
| 16-32 |  | 2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol; aislado como la sal de HCl | 396,1819 |
| 16-33 |  | N-({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)acetamida; aislada como la sal de HCl | 423,1925 |
| 16-34 |  | 4-[3-(2-metilimidazo[1,2-a]piridin-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina | LREM (M+1) = 482,2 |

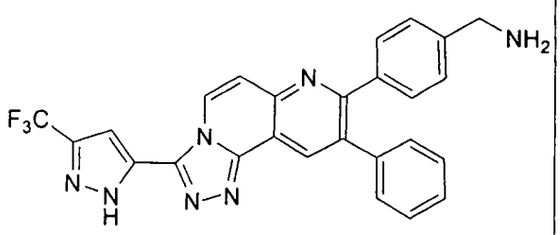
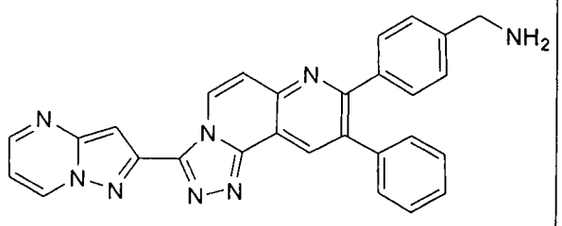
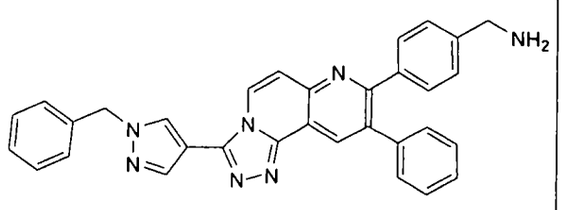
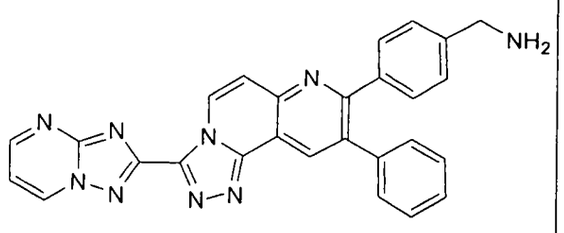
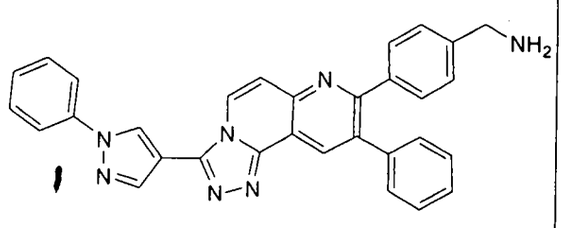
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|---|---|---|---|
| 16-35 |  | 1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil}metanamina | LREM (M+1) = 468,1 |
| 16-36 |  | 1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la base libre y la sal de HCl | 468,1923 |
| 16-37 |  | 1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1,2-benzisoxazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | LREM (M+1)=456,2 [M-NH2] |
| 16-38 |  | 1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la base libre y la sal de HCl | 474,1474 |
| 16-39 |  | 1-{4-[3-(1-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | LREM (M+1)=415,1 [M-NH2] |

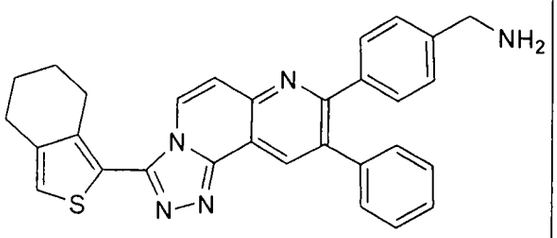
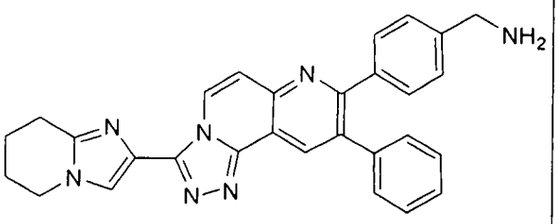
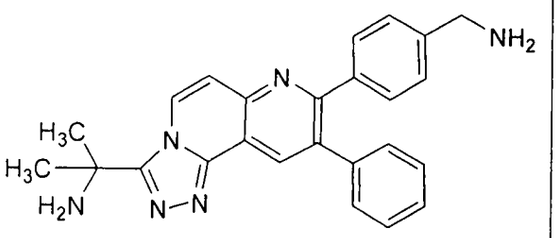
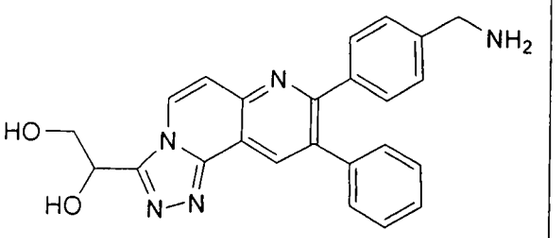
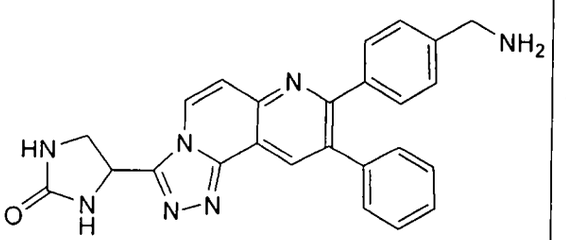
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| 16-40 |  | 1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la base libre y la sal de HCl | LREM (M+1) = 432,1 |
| 16-41 |  | 4-[3-(1-metil-5-fenil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de TFA | 508,2232 |
| 16-42 |  | 1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1-benzotien-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 488,189 |
| 16-43 |  | 1-{4-[3-(1-isopropil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 460,2245 |
| 16-44 |  | 1-{4-[9-fenil-3-(1,4,5,6-tetrahidrociclopenta[c]pirazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 458,2067 |

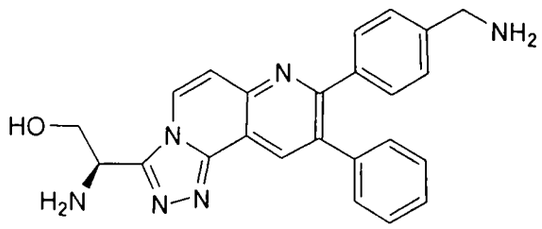
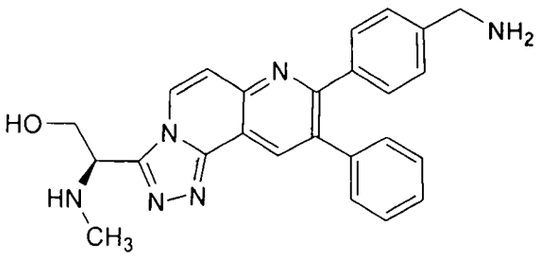
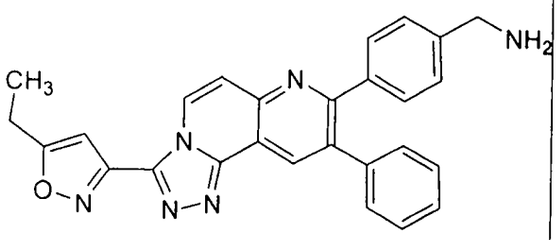
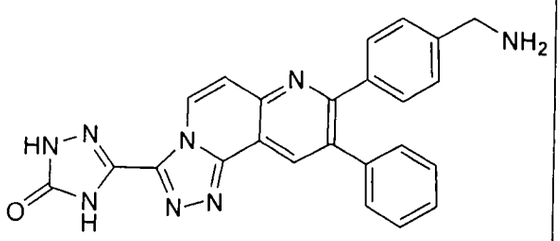
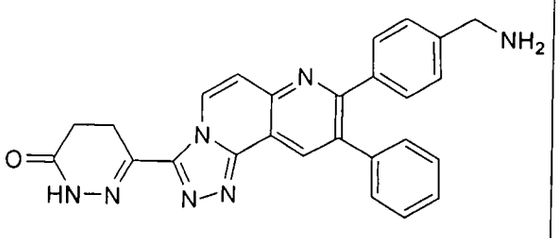
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| 16-45 |  | 1-[4-(9-fenil-3-[(2S)-pirrolidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 421,2137 |
| 16-46 |  | 4-[3-(1-aminoetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de HCl | 395,1962 |
| 16-47 |  | 1-{4-[3-(1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 418,1774 |
| 16-48 |  | 1-[4-(3-ciclopropil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de TFA | 392,1866 |
| 16-49 |  | 1-{4-[9-fenil-3-(trifluorometil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil]metanamina; aislada como la sal de TFA | 420,1423 |

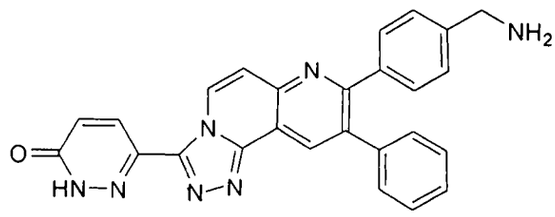
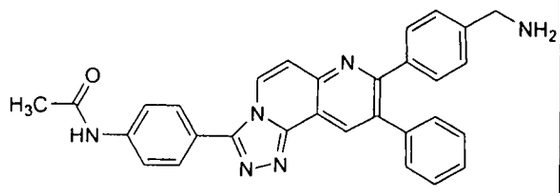
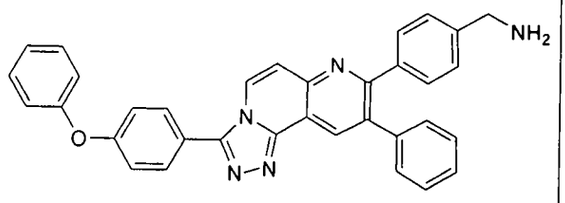
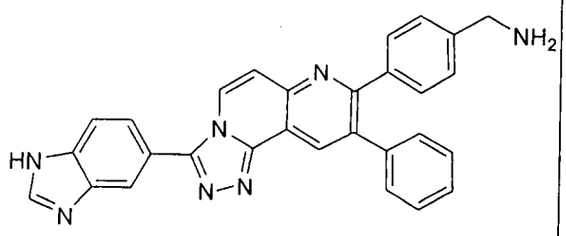
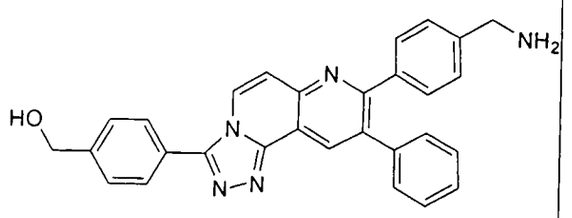
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| 16-50 |  | 1-{4-[3-(5-metil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 432,1924 |
| 16-51 |  | 1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 446,2077 |
| 16-52 |  | 4-[3-(1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de TFA | 467,1968 |
| 16-53 |  | 1-{4-[3-(1-metil-1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 432,1921 |
| 16-54 |  | 1-{4-[3-(3-metil-2H-3lambda$^5$-ilmidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | LREM (M+1) = 432,1 |

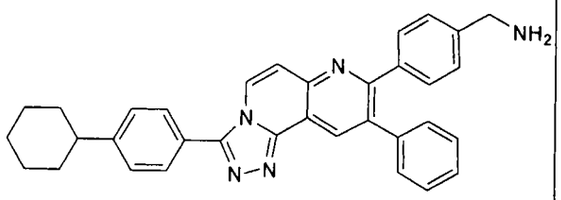
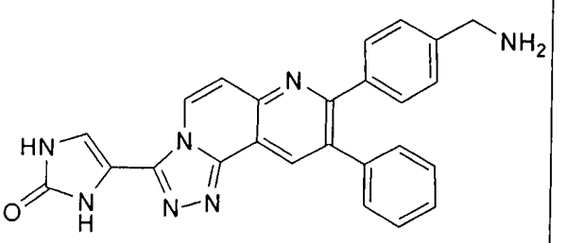
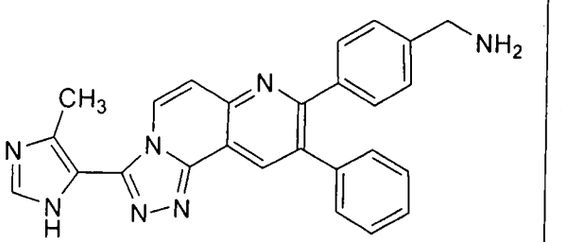
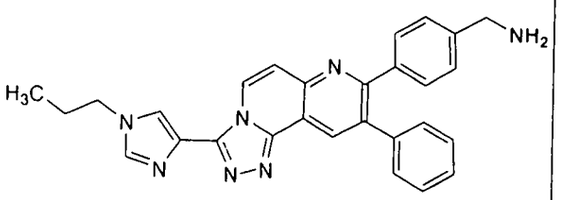
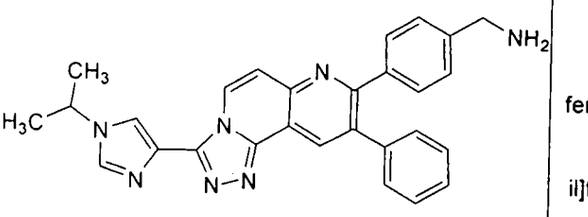
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| 16-55 |  | 4-[3-(6-cloroimidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de TFA | LREM (M+1) = 502,1 |
| 16-56 |  | 1-{4-[3-(1H-bencimidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 468,1921 |
| 16-57 |  | 4-[3-(5-ciclopropil-4H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de TFA | 458,2087 |
| 16-58 |  | 1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1H-indazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 472,2244 |
| 16-59 |  | 4-[9-fenil-3-(3-fenil-1H-pirazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de TFA | 494,2085 |

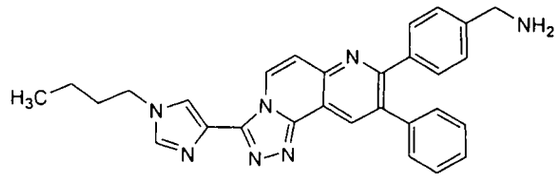
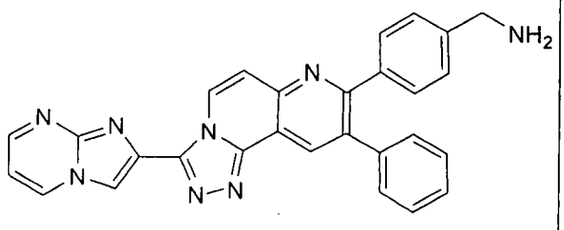
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| 16-60 |  | 1-(4-{9-fenil-3-[3-(trifluorometil)-1H-pirazol-5-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina; aislada como la sal de TFA | 486,1643 |
| 16-61 |  | 1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 469,1881 |
| 16-62 |  | 1-{4-[3-(1-bencil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 508,2235 |
| 16-63 |  | 1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de TFA | 470,1834 |
| 16-64 |  | 4-[9-fenil-3-(1-fenil-1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de TFA | 494,2085 |

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| 16-65 |  | 1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-2-benzotien-1-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de TFA | 488,1901 |
| 16-66 |  | 1-{4-[9-fenil-3-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-2-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 472,2231 |
| 16-67 |  | 2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}propan-2-amina; aislada como la sal de HCl | 409,2126 |
| 16-68 |  | 1-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etano-1,2-diol; aislado como la sal de TFA | 412,1761 |
| 16-69 |  | 4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}imidazolidin-2-ona; aislada como la sal de TFA | 436,1873 |

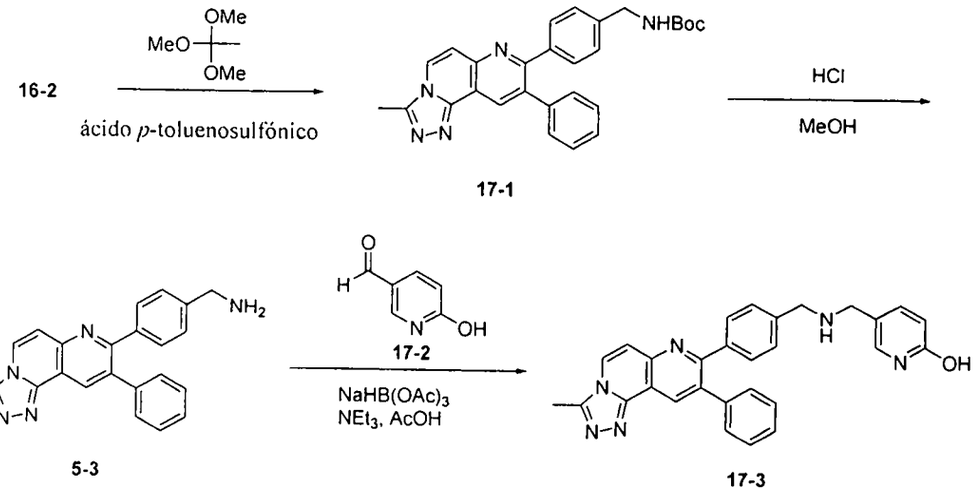
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| 16-70 |  | (2R)-2-amino-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol; aislado como la sal de TFA | 411,1921 |
| 16-71 |  | (2R)-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2-(metilamino)etanol; aislado como la sal de TFA | 425,2077 |
| 16-72 |  | 1-{4-[3-(5-etilisoxazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 447,1913 |
| 16-73 |  | 5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2,4-dihidro-3H-1,2,4-triazol-3-ona; aislada como la sal de HCl | LREM (M+1) = 435,2 |
| 16-74 |  | 6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-4,5-dihidropiridazin-3(2H)-ona; aislada como la sal de HCl | LREM (M+1) = 431,2 [M-NH2] |

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| 16-75 |  | 6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}piridazin-3(2H)-ona; aislada como la sal de HCl | LREM (M+1)=429,1 [M-NH2] |
| 16-76 |  | N-(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)acetamida; aislada como la sal de HCl | 485,2074 |
| 16-77 |  | 1-{4-[3-(4-fenoxifenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 520,2136 |
| 16-78 |  | 1-{4-[3-(1H-bencimidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 468,1927 |
| 16-79 |  | (4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)metanol; aislado como la sal de HCl | 458,1963 |

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| 16-80 |  | 4-[3-(4-ciclohexilfenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}bencilamina; aislada como la sal de HCl | 510,2634 |
| 16-81 |  | 4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-1,3-dihidro-2H-imidazol-2-ona; aislada como la sal de HCl | 434,1719 |
| 16-82 |  | 1-{4-[3-(4-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 432,1921 |
| 16-83 |  | 4-[9-fenil-3-(1-propil-1H-imidazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina; aislada como la sal de HCl | 460,2231 |
| 16-84 |  | 1-{4-[3-(1-isopropil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 460,2231 |

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| 16-85 |  | 1-{4-[3-(1-butil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina; aislada como la sal de HCl | 474,2387 |
| 16-86 |  | 1-[4-(3-imidazo[1,2-a]pirimidin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina; aislada como la sal de HCl | 469,1867 |

ESQUEMA 17




5-({[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil] amino}metil)piridin-2-ol (**17-3**)

4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilcarbamato de *terc*-butilo (**17-1**)

A una solución agitada de **16-2** (5 g, 11,3 mMol) en 20 ml de tolueno:metanol 3:1 se añadió ortoacetato de trimetilo (1,8 g, 15,3 mMol) y ácido *p*-toluenosulfónico monohidrato (0,1 g, 0,6 mMol). La reacción se calentó a 100°C en un reactor de microondas durante 35 minutos. Después de enfriar a temperatura ambiente, se eliminó el disolvente bajo presión reducida. El residuo se purificó usando

cromatografía ultrarrápida en fase normal proporcionando **17-1** como un sólido.
CL/EM (M+1) calculado: 466,6 observado: 466,2

1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil] metanamina (**5-3**)

$HCl_{(g)}$ se hizo burbujear a través de metanol (75 ml) durante 5 min. A esta solución, se añadió **17-1** (7,5 g, 16 mmMol) y la solución se agitó a temperatura ambiente durante 6 horas. Después de eliminar el disolvente *a vacío*, el sólido resultante se trituró durante 30 minutos con una solución 10:1 de acetato de etilo y metanol, respectivamente. La suspensión se filtró y secó proporcionando 5-3 como la sal de HCl. Masa (M+1) calculada: 366,1713 observada: 366,1694

6-hidroxinicotinaldehído (**17-2**)

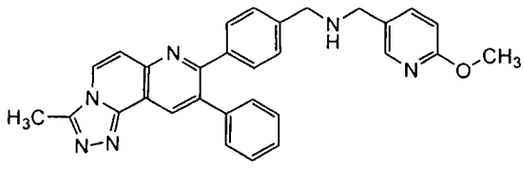
Se calentó una solución agitada de 6-metoxi-3-piridinacarboxaldehído (0,45 g, 3,3 mMol) en HCl 3N (10 ml) a 100°C durante 30 minutos. Tras enfriar, se desarrollaron cristales similares a agujas. Los cristales se recogieron por medio de filtración proporcionando **17-2**. RMN-$^1$H ($CD_3OD$) δ 9,64 (s, 1H), δ 8,17-8,16 (m, 1H), δ 7,96-7,94 (m, 1H), δ 6,58 (d, 1H).

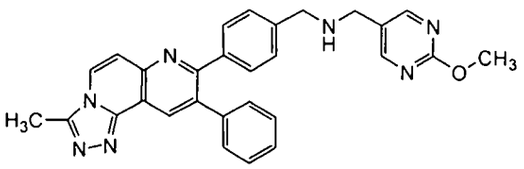
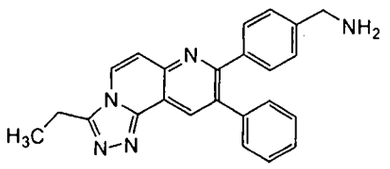
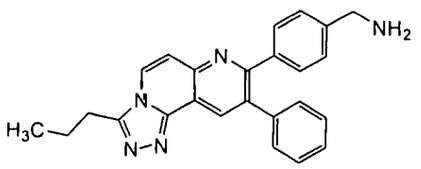
5-({[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil] amino}metil)piridin-2-ol (**17-3**)

A una solución agitada de 5-3 (0,1g, 0,3 mMol) y trietilamina (0,08 ml, 0,5 mMol) en RMN (1 ml) se añadió 17-2 (0,03 g, 0,3 mMol) y ácido acético (0,03 ml, 0,5 mMol), seguido por triacetoxiborohidruro de sodio (0,12 g, 0,5 mMol). Después de agitar durante toda una noche a temperatura ambiente, la reacción se filtró a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 proporcionando **17-3** como la sal de HCl. Masa (M+1) calculada: 473,2085 observada: 473,2092.

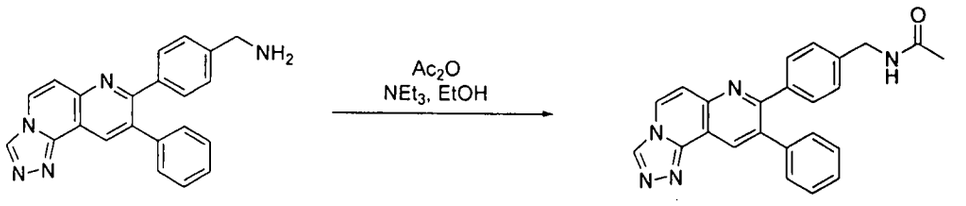
La siguiente tabla (Tabla 7) contiene compuestos fabricados usando los procedimientos de Esquema 17, sustituyendo el aldehído apropiado por **17-2**. Se aislaron compuestos **17-4** y **17-5** como sales de HCl. Se aislaron compuestos **17-6** y **17-7** como sales de TFA.

Tabla 7

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **17-4** |  | 1-(6-metoxipiridin-3-il)-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]metanamina | 487,2237 |

| | | | |
|---|---|---|---|
| 17-5 |  | N-[(2-metoxipirimidin-5-il)metil]-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amina | LREM (M+1)= 488,1 |
| 17-6 |  | 1-[4-(3-etil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil] metanamina (5-3) | LREM (M+1)= 380,2 |
| 17-7 |  | 1-[4-(9-fenil-3-propil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina | 394,2023 |

ESQUEMA 18

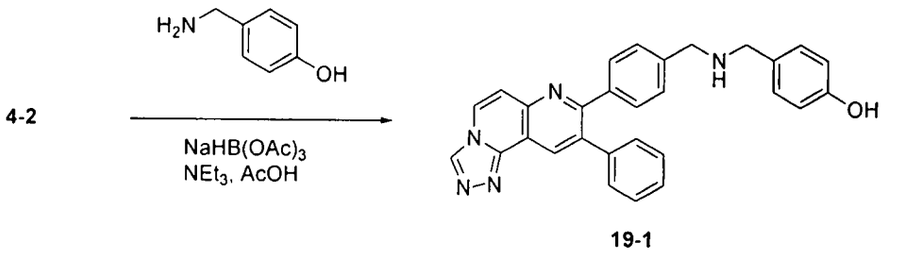



**4-3** **18-1**

N-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil] acetamida (**18-1**)

A una solución de **4-3** (0,02 g, 0,06 mMol) y trietilamina (0,02 ml, 0,2 mMol) en etanol absoluto (0,5 ml) se añadió anhídrido acético (0,02 ml, 0,2 mMol). La reacción se completó después de 10 minutos y se purificó directamente en una HPLC de fase reversa de C18 dando **18-1** como un sólido. CL/EM (M+1) calculado: 394,5; observado: 394,2.

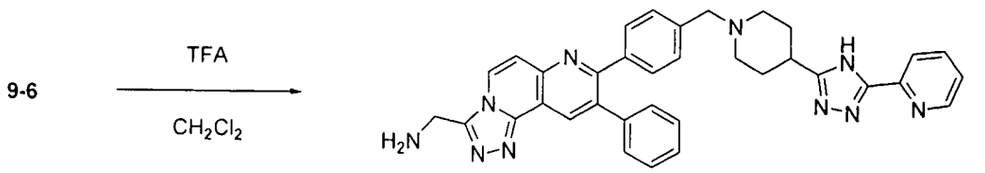
ESQUEMA 19




**19-1**

4-({[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amino}metil)fenol (**19-1**) A una solución agitada de 4-2 (0,05 g, 0,14 mMol) y 4-(aminometil)fenol (0,04, 0,35 mMol) en DMF (0,5 ml) se añadió ácido acético (0,04 ml, 0,7 mMol). Después de agitar durante 2 horas a temperatura ambiente, se añadió triacetoxiborohidruro de sodio (0,06 g, 0,3 mMol). Después de agitar durante toda una noche, la solución se filtró a través de un filtro de jeringuilla y se purificó en una HPLC de fase reversa de C18 dando **19-1** como un sólido. CL/EM (M+1) calculado: 458,5; observado: 458,3.

ESQUEMA 20

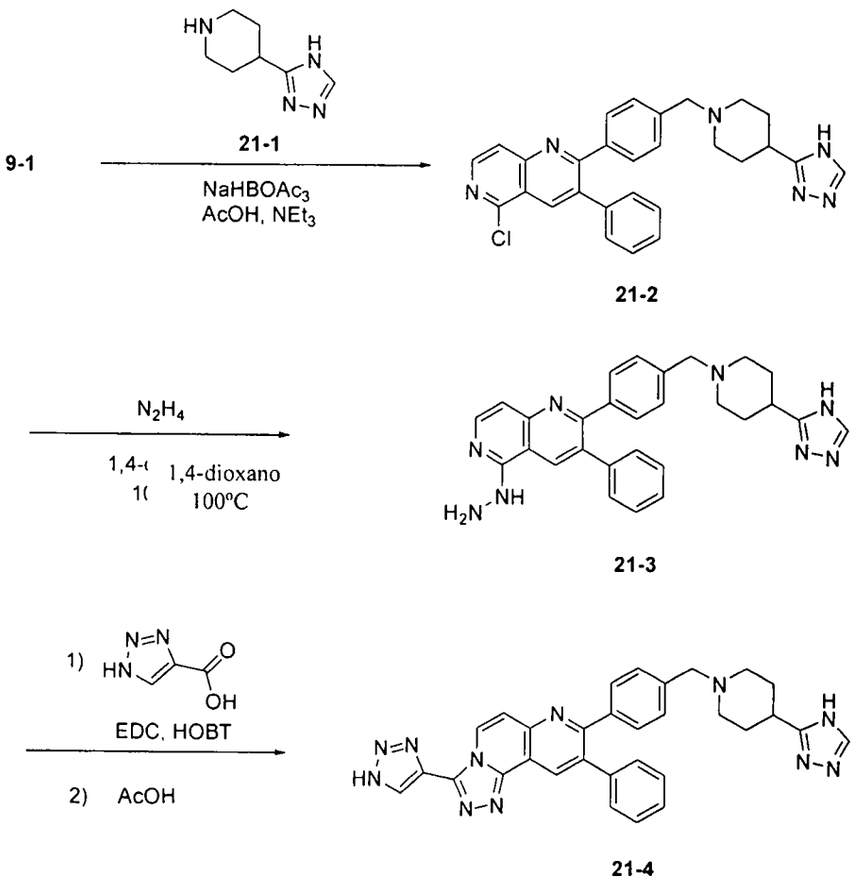



**20-1**

1-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanamina (**20-1**)

Una solución de **9-6** (0,03 g, 0,04 mMol) en TFA al 30% en diclorometano (1 ml, 30% en volumen) se agitó a temperatura ambiente durante 30 minutos. El disolvente se eliminó *a vacío* y el residuo en bruto se llevó en metanol y se purificó en una HPLC en fase reversa de C18 dando **20-1** como un sólido. Masa (M+1) calculada: 593,2884; observada: 593,2867.

ESQUEMA 21




9-fenil-3-(1H-1,2,3-triazol-4-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**21-4**)

4-(1*H*-1,2,4-triazol-3-il)piperidina (**21-1**)

A una solución de 4-cianopiperidina-1-carboxilato de bencilo (20 g, 82 mmol) en metanol (150 ml) se añadió una solución de metóxido de sodio en metanol (25% en peso, 5,6 ml, 25 mmol) a temperatura ambiente. Después de 30 minutos, se añadió una solución de hidracida fórmica (4,9 g, 82 mmol) en metanol (20 ml) y la reacción se calentó a reflujo durante 24 horas, tiempo al cual se añadieron metóxido de sodio en metanol (25% en peso, 5,6 ml, 25 mmol) e hidrazida fórmica (4,9 g, 82 mmol). Después de 72 horas, la reacción se enfrió a

temperatura ambiente y se desactivó con ácido acético (3,0 ml, 49 mmol) y se concentró. El residuo resultante se disolvió en acetato de etilo, se lavó con agua, bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. El residuo se purificó mediante cromatografía en columna que eluyendo con IPA/DCM 1-35%. Las fracciones apropiadas se combinaron y el disolvente se eliminó a vacío dando 4-(1*H*-1,2,4-triazol-3-il)piperidina-1-carboxilato de bencilo como un sólido. EM ($M+H^+$): 287,2; RMN-$^1$H (400 MHz, $CDCl_3$): δ 11,13 (s, 1H), 8,06 (s, 1H), 7,36-7,31 (m, 5H), 5,15 (s, 2H), 4,24 (s.a., 2H), 3,06-2,98 (m, 3H), 2,07-2,04 (m, 2H), 1,84-1,78 (m, 2H).

A una solución de 4-(1*H*-1,2,4-triazol-3-il)piperidina-1-carboxilato de bencilo (7,3 g, 25 mmol) en etanol (100 ml) se añadió paladio al 10% en carbono (500 mg) y el recipiente de reacción se purgó con hidrógeno y se agitó sobre una atmósfera de hidrógeno durante 3 horas. La reacción se filtró y concentró dando **21-1** como un sólido. EM ($M+H^+$): 153,2; RMN-$^1$H (400 MHz, DMSO-$d_6$): δ 7,99 (s, 1H), 2,98-2,94 (m, 2H), 2,82-2,74 (m, 1H), 2,57-2,50 (m, 2H), 1,82-1,78 (m, 2H), 1,60-1,50 (m, 2H).

5-cloro-3-fenil-2-(4-{[4-(4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**21-2**)

A una solución agitada de **9-1** (0,25 g, 0,73 mMol) y **21-1** (0,13 g, 0,87 mMol) en NMP (5 ml) se añadió trietilamina (0,3 ml, 2,2 mMol) seguida por ácido acético (0,082 ml, 1,5 mMol). Después de agitar a temperatura ambiente durante toda una noche, se añadió triacetoxiborohidruro de sodio (0,18 g, 0,87 mMol). Tras completación, la reacción se diluyó con acetato de etilo y se lavó con $NaHCO_3$ saturado, seguido por agua, después salmuera. La fase orgánica se secó con $Na_2SO_4$ y $MgSO_4$, se filtró y se concentró *a vacío* proporcionando **21-2**. CL/EM (M+1) calculado: 482,0; observado: 482,2

5-hidrazino-3-fenil-2-(4-{[4-(4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-1,6-naftiridina (**21-3**)

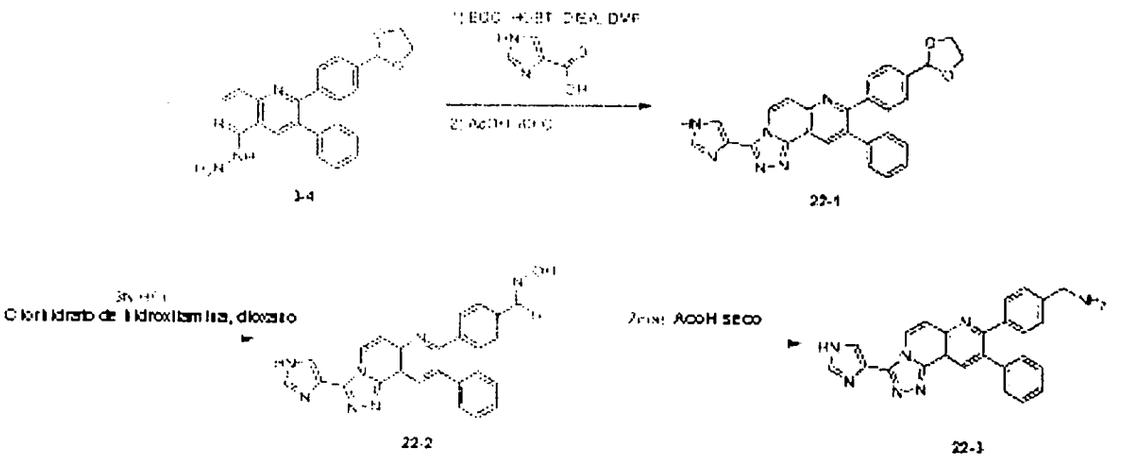
A una solución agitada de **21-2** (0,4 g, 0,8 mMol) en 1,4-dioxano anhidro (3 ml) se añadió hidrazina (0,45 ml, 14,5 mMol). La solución se calentó a 100°C en un reactor de microondas durante 5 minutos. El disolvente se retiró *a vacío* y se secó azeotrópicamente con tolueno tres veces proporcionando **21-3**. CL/EM (M+1) calculado: 477,6; observado: 477,3

9-fenil-3-(1H-1,2,3-triazol-4-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**21-4**)

A una solución agitada de **21-3** (0,2 g, 0,36 mMol), HOBT (0,05 g, 0,4 mMol), y ácido 1H-1,2,3-triazol-4-carboxílico (0,05 g, 0,4 mMol) en DMF anhidro (2 ml) se añadió DIEA (0,18 ml, 1,1 mMol) seguido por EDC (0,08 g, 0,4 mMol). La solución se calentó en el reactor de microondas durante 12 minutos a 80°C. La solución se trató después con 0,5 ml de ácido acético y se calentó a 80°C en el reactor de microondas durante 10 minutos adicionales. Tras enfriar a temperatura ambiente, la solución se hizo pasar a través de un filtro de jeringuilla

y se purificó en una HPLC de fase reversa de C18 proporcionando **21-4** como la sal de HCl. Masa (M+1) calculada: observada: CL/EM (M+1) calculado: 554,6; observado: 554,3.

ESQUEMA 22



1-{4-[3-(1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-3**)

8-[4-(1,3-dioxolan-2-il)fenil]-3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridina (**22-1**)

A una solución **3-4** (0,2 g, 0,5 mmol), ácido 1H-imidazol-4-carboxílico (0,06 g, 0,5 mmol), HOBT (0,06 g, 0,5 mmol), y DIEA (0,2 ml, 1,4 mmol) en DMF (2 ml) se añadió EDC (0,1g, 0,6 mmol). La solución se agitó a temperatura ambiente durante 45 minutos y se calentó después a 80°C en el microondas durante 15 minutos. El disolvente se eliminó a vacío. El residuo se llevó en DMF (0,5 ml) y se trató con AcOH glacial (2,0 ml). La mezcla de reacción se calentó a 80°C durante 45 min. La reacción se desactivó después con agua (10 ml) y se extrajo dentro de EtOAc (3 x 20 ml). Las fases orgánicas combinadas se concentraron a vacío dando **22-1** como un residuo marrón.

EM calculado M+H: 461,5, hallado 461,2.

4-[3-(1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]benzaldehído oxima (**22-2**)

A una solución de **22-1** (0,8 g, 1,7 mmol) en 1,4-dioxano (3 ml) se añadió HCl 3N (1,1 ml, 3,4 mmol) gota a gota. Después de agitar durante 10 minutos la solución se trató con clorhidrato de hidroxilamina (0,5 g, 6,9 mmol) en agua (0,5 ml). La mezcla se agitó durante 1 hora y se desactivó después con $NaHCO_3$(s) hasta pH=8. Tras la eliminación del disolvente el residuo se llevó en agua, se filtró y se secó azeotrópicamente con tolueno proporcionando **22-2** como un sólido.

EM calculado M+H: 432,5, hallado 432,2.

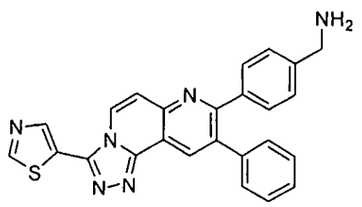
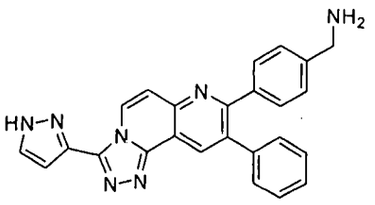
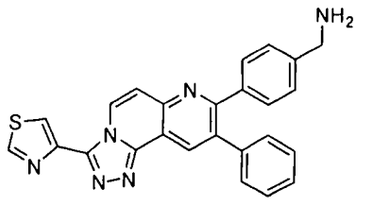
1-{4-[3-(1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina (**22-3**)

Una solución de **22-2** (0,06, 0,1 mmol) y Zn(s) (0,02 g, 0,3 mmol) en AcOH glacial seco se agitó a temperatura ambiente durante 30 min. Se añadieron a la solución otros 4 equivalentes de Zn(s) (0,04 g, 0,6 mmol). La mezcla de reacción se agitó durante 1 hora adicional. Después de filtración y eliminación del disolvente el residuo se llevó en MeOH y se trató con hidróxido de amonio. Tras la eliminación del disolvente, el residuo se purificó mediante HPLC en fase reversa dando **22-3** como un sólido.

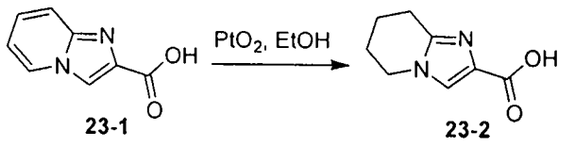
EM calculado M+H: 418,5, hallado 401,1 ($M-NH_2$).

La siguiente tabla (Tabla 8) contiene compuestos fabricados usando los procedimientos de Esquema 22 sustituyendo el ácido apropiado por el imidazol-4-carboxílico. Los compuestos en Tabla 8 se aislaron como la sal de HCl.

Tabla 8

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **22-4** |  | 1-{4-[9-fenil-3-(3H-1lambda$^4$,3-tiazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | 437,1543 |
| **22-5** |  | 1-{4-[9-fenil-3-(1H-pirazol-3-il)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | 418,1776 |
| **22-6** |  | 1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | 435,1385 |

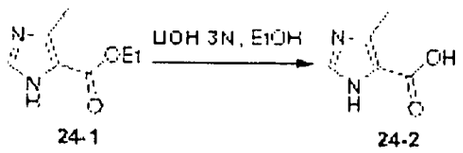
ESQUEMA 23




Ácido 5,6,7,8-tetrahidroimidazo[1,2-a]piridina-2-carboxílico (**23-2**)

A una solución de **23-1** (0,1 g, 0,7 mmol) en EtOH (15 ml) en un matraz secado se añadió $Pt_2O$ (0,1g, 0,4 mmol). La mezcla de reacción se situó bajo una atmósfera de nitrógeno y se evacuó subsiguientemente. Esto se repitió 3 veces antes de situar la mezcla de reacción bajo una atmósfera de hidrógeno. Después de 3 horas la mezcla de reacción se filtró a través de celite. Tras la eliminación de disolvente se obtuvo el producto deseado **23-2** como un polvo blanquecino. EM calculado M+H: 167,2, hallado 167,1.

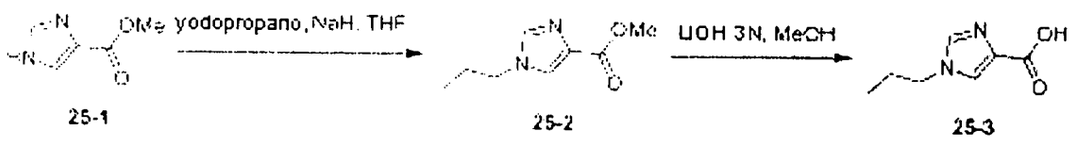
ESQUEMA 24




Ácido 4-metil-1H-imidazol-5-carboxílico (**24-2**)

A una solución de **24-1** (0,5 g, 2,4 mmol) en EtOH (2 ml) se añadió LiOH 3N (2,2 ml, 6,5 mmol). La mezcla de reacción se calentó a 80°C durante 1 hora. El calor se redujo a 40°C y la mezcla se agitó durante toda una noche. La mezcla se trató después a 80°C durante unas 5,5 horas adicionales. La reacción se neutralizó con HCl 12N y se concentró a vacío. El residuo se secó azeotrópicamente con tolueno proporcionando el producto deseado **24-2** como un sólido. EM calculado M+H: 127,1, hallado 127,1

ESQUEMA 25




1-propil-1H-imidazol-4-carboxilato de metilo (**25-2**)

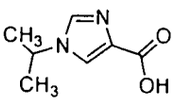
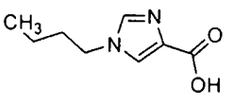
A una solución de **25-1** (0,5 g, 4,0 mmol) en THF anhidro (15 ml) en un matraz seco se añadió NaH (0,1g, 4,8 mmol) por partes. Una vez que el burbujeo ha bajado se añadió yodopropano (0,8ml, 8,0 mmol) y se agitó a temperatura ambiente durante toda una noche. A la

mezcla de reacción se añadieron otros 0,5 eq de NaH junto con 3 eq de yodopropano. Después de agitar durante 50 h se añadieron otros 0,5 eq de NaH junto con 2 eq de yodopropano. La mezcla de reacción se agitó durante 20 horas antes de desactivarse con etanol (5 ml). La eliminación del disolvente proporcionó el producto deseado **25-2** como un sólido.
EM calculado M+H: 169,2, hallado 155,1 ($M-CH_2$).

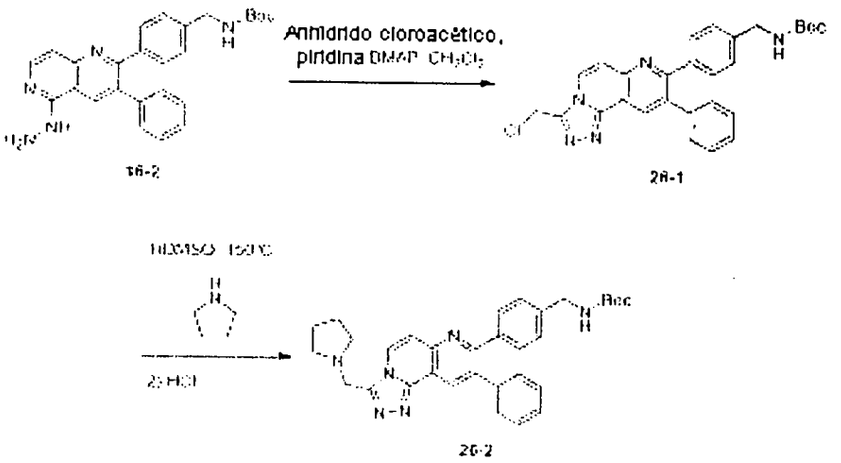
Ácido 1-propil-1H-imidazol-4-carboxílico (**25-3**)

A una solución de **25-2** (0,6 g, 3,6 mmol) en MeOH anhidro (2 ml) se añadió LiOH 3N (2,6 ml, 7,9 mmol). La mezcla de reacción se calentó a 80°C durante 1 hora. El calor se redujo y la mezcla se agitó a 40°C durante toda una noche. La reacción se neutralizó después con HCl 12N y se concentró subsiguientemente a vacío. El residuo se secó azeotrópicamente con tolueno proporcionando el producto deseado **25-3** como un sólido. EM calculado M+H: 155,2, hallado 155,1

La siguiente tabla (Tabla 9) contiene compuestos fabricados usando los procedimientos de Esquema 25 sustituyendo el haluro de alquilo apropiado.
Tabla 9

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **25-4** |  | Ácido 1-isopropil-1H-imidazol-4-carboxílico | 155,1 |
| **25-5** |  | Ácido 1-butil-1H-imidazol-4-carboxílico | 155,1 |

ESQUEMA 26




4-[9-fenil-3-(pirrolidin-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina (**26-2**)

4-[3-(clorometil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilcarbamato de terc-butilo (**26-1**)

A una suspensión de **16-2** (1,2 g, 2,7 mmol) en $CH_2Cl_2$ (10 ml) se añadió DMAP (0,03 g, 0,03 mmol) y piridina (0,4 ml, 5,4 mmol) seguido por anhídrido cloroacético (0,5 g, 3,0 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas antes de añadir anhídrido cloroacético adicional (0,2 g, 0,9 mmol). Se eliminó el disolvente a vacío después de agitar durante 10 minutos adicionales. El residuo se fraccionó entre $NaHCO_3$ acuoso saturado y EtOAc (3 x 30 ml). Las fases orgánicas combinadas se lavaron con agua, salmuera y se secaron ($Na_2SO_4/MgSO_4$). La eliminación del disolvente proporcionó el producto deseado **26-1** como un polvo rojo. EM calculado: 500,2, hallado 500,1.

4-[9-fenil-3-(pirrolidin-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina

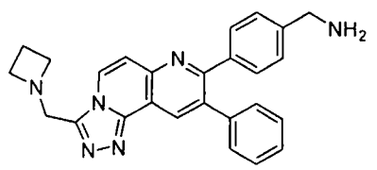
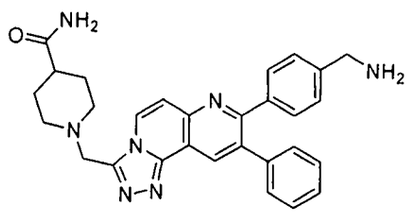
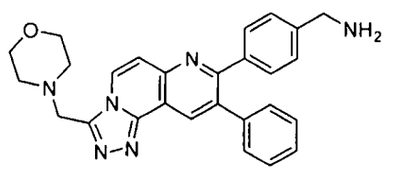
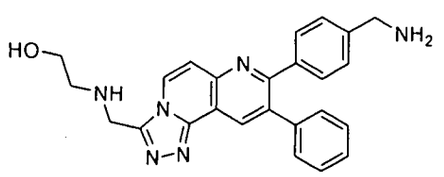
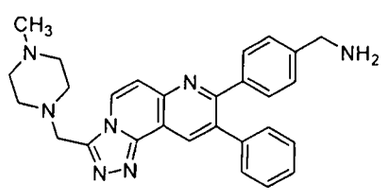
(**26-2**)

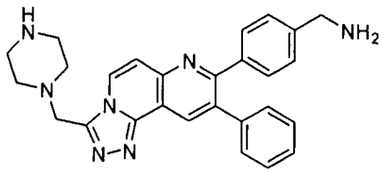
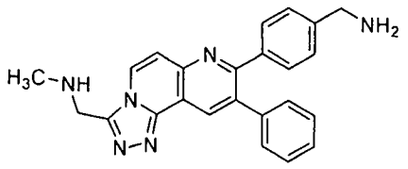
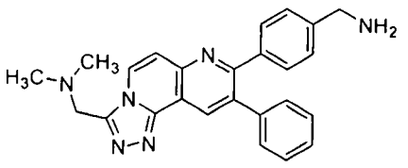
A una solución de **26-1** (0,05 g, 0,1 mmol) en DMSO (1 ml) se añadió pirrolidina. La solución se calentó a 150°C durante 30 min. La mezcla de reacción se purificó usando HPLC en fase reversa. El residuo se disolvió en MeOH (0,5 ml) y se trató con HCl 1N (0,4 ml). La mezcla de reacción se calentó a 35°C durante 1 hora. La eliminación del disolvente proporcionó el producto deseado **26-2** como un sólido.

EM calculado: 535,7, 435,5

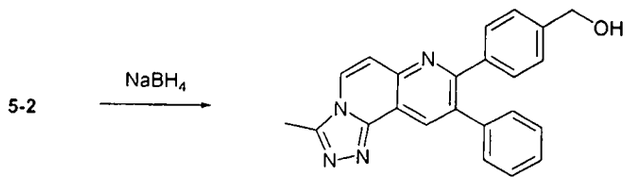
La siguiente tabla (Tabla 10) contiene compuestos preparados usando los procedimientos de Esquema 26 sustituyendo la amina apropiada por pirrolidina. Los compuestos en Tabla 10 se aislaron como sales de HCl.

Tabla 10

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **26-3** |  | 1-{4-[3-(acetidin-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | 421,2124 |
| **26-4** |  | 1-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)piperidina-4-carboxamida | 492,249 |
| **26-5** |  | 1-{4-[3-(morfolin-4-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina | 451,2228 |
| **26-6** |  | 2-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)amino]etanol | 425,2071 |
| **26-7** |  | 1-(4-{3-[(4-metil piperazin-1-il)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina | 464,2543 |

| | | | |
|---|---|---|---|
| **26-8** |  | 4-[9-fenil-3-(piperazin-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina | 450,2386 |
| **26-9** |  | N-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)-N-metilamina | 395,1969 |
| **26-10** |  | N-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)-N,N-dimetilamina | 409,2125 |

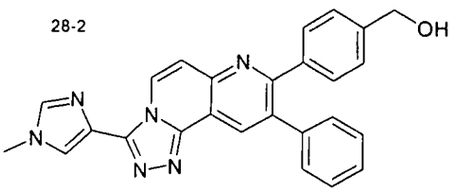
ESQUEMA 28




4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)fenil] metanol (**28-1**)

A una solución de 4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)benzaldehído (5-2, 0,317 g, 0,870 mmol) en metanol (5 ml) se añadió borohidruro de sodio (0,033 g, 0,870 mmol) a 0°C. Después de 10 minutos, la mezcla de reacción se vertió en acetato de etilo, y la fase orgánica se lavó con una solución saturada de bicarbonato de sodio, agua, después salmuera, se secó sobre sulfato de sodio, se filtró y se concentró hasta sequedad bajo presión reducida. La purificación mediante cromatografía en fase reversa (Waters Sunfire MSC18, acetonitrilo al 1%/ácido trifluoroacético al 0,1%/agua → acetonitrilo al 95%/ácido trifluoroacético al 0,1%/agua) dio los compuestos del título como un sólido. HREM ($M+H^+$): calculado = 367,1554, observado = 367,1547.

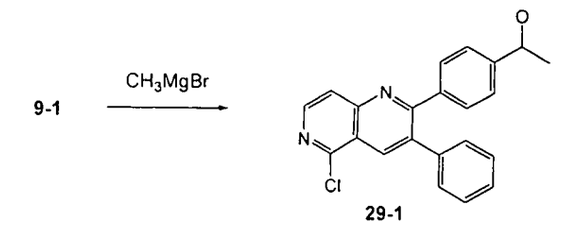
28-2



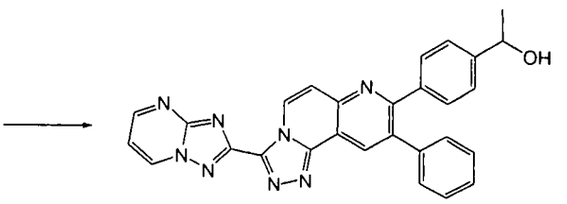
{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}metanol (**28-2**)

El compuesto del título se preparó a partir de **13-2** de acuerdo con el procedimiento de Esquema 28; HREM ($M+H^+$): calculado = 433,1772, observado = 433,1761.

ESQUEMA 29



**29-1**



**29-2**

1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*]pirimidin-2-il[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanol (**29-2**)

1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]etanol (**29-1**)

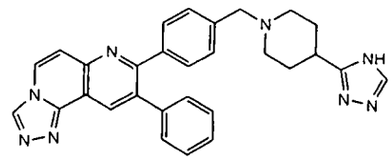
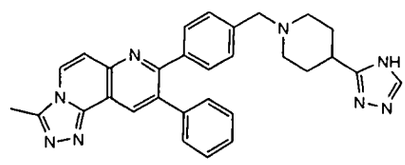
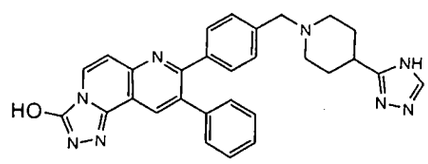
A una solución de 4-(5-cloro-3-fenil-1,6-naftiridin-2-il)benzaldehído (**9-1**, 0,500 g, 1,450 mmol) en cloruro de metileno anhidro (10 ml) se añadió bromuro de metilmagnesio (2,072 ml, 2,9 mmol, 1,4M en tolueno/tetrahidrofurano (75:25)) a 0 °C. Después de 15 minutos, la mezcla de reacción se vertió en acetato de etilo, y la fase orgánica se lavó con una solución saturada de bicarbonato de sodio, agua, después salmuera, se secó sobre sulfato de sodio, se filtró y se concentró hasta sequedad bajo presión reducida dando el compuesto del título. EM ($M+H^+$): calculado = 361,85, observado = 361,1.

1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*]pirimidin-2-il[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanol (**29-2**)

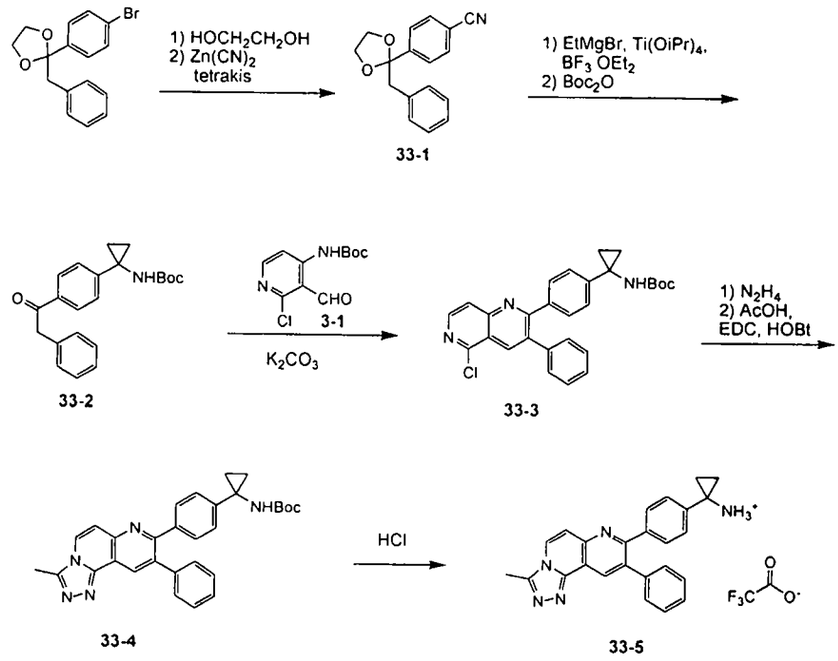
El compuesto del título se preparó de acuerdo con los procedimientos del esquema 9; HREM ($M+H^+$): calculado = 485,1833, observado = 485,1812.

Los siguientes compuestos en la tabla 11 se prepararon de acuerdo al procedimiento de esquema 13 de piperidina **21-1** y el aldehído indicado.

Tabla 11

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **30-1** **(de 4-2)** |  | 9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina | Calc.: 487,2353 Observado: 484,2371 |
| **31-1** **(de 5-2)** |  | 3-metil-9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl | Calc.: 501,2510 Observado: 501,2531 |
| **32-1** **(de 3-6)** |  | 9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-3-ol | Calc.: 503,2303 Observado: 503,2327 |

ESQUEMA 33




Trifluoroacetato de 1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil] ciclopropilaminio (**33-5**)

4-(2-bencil-1,3-dioxolan-2-il)benzonitrilo (**33-1**)

Una solución de 1-(4-bromofenil)-2-feniletanona (5,0 g, 18 mmol), etilenglicol (3,0 ml, 54 mmol) y ácido tósico (0,04 g, 0,2 mmol) en tolueno (30 ml) se calentó a reflujo con un trampa de Dean-Stark durante 15 horas. La reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo, se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró dando 2-bencil-2-(4-bromofenil)-1,3-dioxolano en bruto como un sólido blanco. Al material orgánico se añadió cianuro de cinc (2,3 g, 20 mmol), tetrakis(trifenilfosfina)paladio (3,3 g, 2,8 mmol), DMF (20 ml) y dioxano (20 ml) y la suspensión resultante se purgó con nitrógeno durante 15 minutos antes de calentarse 100°C durante 15 horas. La reacción se enfrió a temperatura ambiente, se vertió en éter y se filtró. El filtrado orgánico se lavó con agua, bicarbonato saturado, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en gel de sílice (acetato de etilo al 1%/hexano → acetato de etilo al 50% / hexano) dio el compuesto del título como un sólido blanco. EM ($M+H^+$): calculado = 265,31, observado = 266,1.

{1-[4-(fenilacetil)fenil]ciclopropil}carbamato de *terc*-butilo (**33-2**)

A una solución de 4-(2-bencil-1,3-dioxolan-2-il)benzonitrilo (**33-1**, 1,5 g, 5,6 mmol) en éter (25 ml) se añadió isopropóxido de titanio (1,8 ml, 6,2 mmol) seguido por bromuro de etilmagnesio (4,2 ml, 12 mmol, 3M en éter) a -78°C. Después de 10 minutos, la reacción se calentó a temperatura ambiente durante 60 minutos. La reacción se enfrió a 0°C y se

añadió complejo eterato de trifluoruro de boro (1,4 ml, 11 mmol). Después de 30 minutos a 0°C, la reacción se calentó a temperatura ambiente durante 1 hora tiempo al cual la reacción se desactivó y acidificó con HCl 1M. La suspensión se agitó durante unas 3 horas adicionales a temperatura ambiente, tiempo al cual la mezcla se basificó con NaOH 1 M y se extrajo con cloroformo. Los productos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y se concentraron. Al material orgánico se añadió inmediatamente acetonitrilo (15 ml) y dicarbonato de di-terc-butilo (1,2 g, 5,6 mmol) a temperatura ambiente. Después de 12 horas, la reacción se concentró a sequedad y se purificó mediante cromatografía en gel de sílice (acetato de etilo al 1%/hexano → acetato de etilo al 60%/hexano) dando el compuesto del título como un sólido blanco. EM ($M+H^+$): calculado = 351,44, observado = 352,1.

{1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]ciclopropil}carbamato de *terc*-butilo (**33-3**)

Una solución de **33-2** (0,64 g, 2,5 mmol), 3-1 (0,88 g, 2,5 mmol) y carbonato de potasio (2,1 g, 15 mmol) en DMF (14 ml) se calentó a 120°C durante 4,5 horas. La reacción se enfrió a temperatura ambiente, se diluyó con acetato de etilo, se lavó con agua, salmuera, se secó sobre sulfato de sodio, se filtró y se concentró. La purificación mediante cromatografía en gel de sílice (acetato de etilo al 1%/hexano → acetato de etilo al 70%/hexano) dio el compuesto del título como un sólido blanco. EM ($M+H^+$): calculado = 471,98, observado = 472,1.

1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]ciclopropilcarbamato de *terc*-butilo (**33-4**)

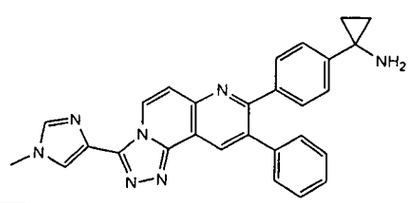
El compuesto del título se preparó a partir de 33-3 de acuerdo con el procedimiento del Esquema 27; EM ($M+H^+$): calculado = 491,58, observado = 492,1.

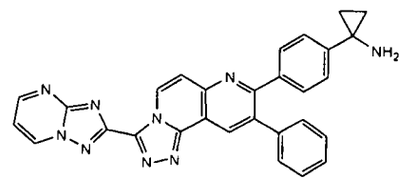
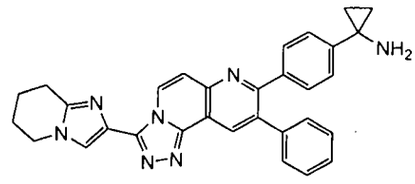
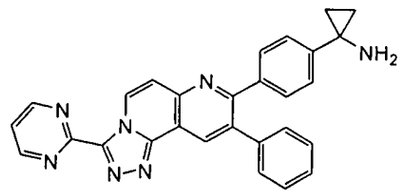
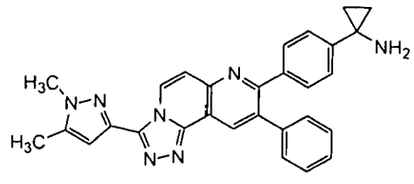
Trifluoroacetato de 1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil] ciclopropilaminio (**33-5**)

El compuesto del título se preparó de acuerdo con el procedimiento del esquema 27; HREM ($M+H^+$): calculado = 392,1870, observado = 392,1893.

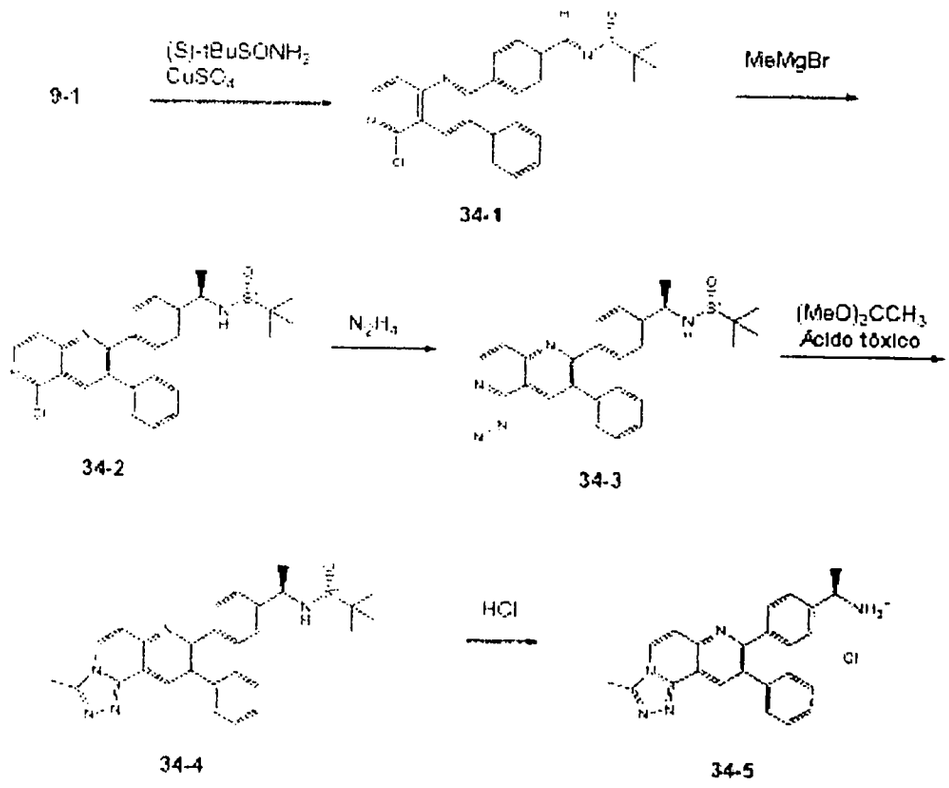
Los siguientes compuestos en la Tabla 12 se prepararon de acuerdo con el procedimiento de Esquema 33. Se aislaron compuestos **33-8** – **33-10** como sales de HCl. Se aisló compuesto **33-6** como una sal de TFA.

Tabla 12

| Cmp | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **33-6** |  | 1-{4-[3-(1-metil-1*H*-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}ciclopropanamina | Calc.: 458,2088 Observado: 458,2114 |

| | | | |
|---|---|---|---|
| 33-7 |  | 1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*]pirimidin-2-il[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropanamina | Calc.: 496,1993<br>Observado: 496,1987 |
| 33-8 |  | 1-{4-[9-fenil-3-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-2-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}ciclopropanamina | 498,238 |
| 33-9 |  | 1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]ciclopropanamina | 456,1915 |
| 33-10 |  | 1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}ciclopropanamina | 472,2227 |

ESQUEMA 34




Cloruro de (1R)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanaminio (**34-5**)

*N*-{(1*E*)-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]metileno}-2-metilpropano-2-sulfinamida (34-1)

Una solución de 4-(5-cloro-3-fenil-1,6-naftiridin-2-il)benzaldehído (**9-1**, 4,24 g, 12,3 mmol), S-(-)-2-metilpropano-2-sulfinamida (3,43 ml, 28,3 mmol) y sulfato cúprico (4,49 g, 28, 1 mmol) en cloruro de metileno (20 ml) se calentó a reflujo bajo una atmósfera de nitrógeno. Después de 18 horas, la reacción se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía en gel de sílice (acetato de etilo al 0%/hexano → acetato de etilo al 45%/hexano) dio el compuesto del título como una espuma naranja. EM ($M+H^+$): calculado = 447,99, observado = 448,2.

*N*-{(1*R*)-1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]etil}-2-metilpropano-2-sulfinamida (**34-2**)

A una solución de *N*-{(1*E*)-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]metileno}-2-metilpropano-2-sulfinamida (**34-1**, 4,53 g, 10,1 mmol) en cloruro de metileno (100 ml) se añadió bromuro de metilmagnesio (30 ml, 42,0 mmol, 1,4M en tolueno:THF 75:25) a -10°C. Después de 30 minutos, la

reacción se desactivó mediante adición de solución de cloruro de amonio saturada (manteniendo mientras la temperatura por debajo de 0°C) y se extrajo con cloruro de metileno. Los productos orgánicos combinados se lavaron con agua, salmuera, se secaron sobre sulfato de magnesio, se filtraron y concentraron dando el compuesto del título como un sólido amarillo pálido.EM ($M+H^+$): calculado = 464,03, observado = 464,2.

({(1*R*)-1-[4-(5-hidrazino-3-fenil-1,6-naftiridin-2-il)fenil]etil}amino)sulfoniumolato de *terc*-butilo (**34-3**)

A una solución de una *N*-{(1*R*)-1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]etil}-2-metilpropano-2-sulfinamida (**34-2**, 0,707 g, 1,52 mmol) y hidrazina anhidra (15 ml) se calentó a 115°C durante 1 hora. La mezcla de reacción se vertió en acetato de etilo, y la fase orgánica se lavó con una solución saturada de bicarbonato de sodio, después agua, después salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró a sequedad bajo presión reducida dando el aducto de hidrazina en bruto como un sólido naranja. EM ($M+H^+$): calculado = 459,62, observado = 460,4.

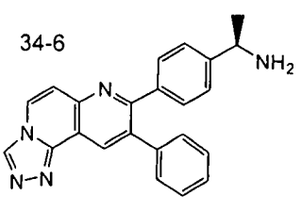
({[1*R*-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etil}animo)sulfoniumolato de *terc*-butilo(**34-4**)

A ({(1*R*)-1-[4-(5-hidrazino-3-fenil-1,6-naftiridin-2-il)fenil]etil}amino)sulfoniumolato de *terc*-butilo en bruto (**34-3**, 1,06 g, 2,31 mmol), ácido p-toluenosulfónico (63 mg, 0,36 mmol), y trimetilortoacetato (1,0 ml, 7,7 mmol) se añadió tolueno anhidro (10 ml) y se calentó a 110°C durante 48 horas. La mezcla de reacción se redujo bajo presión reducida y mediante cromatografía en gel de sílice (metanol al 0-10%/cloruro de metileno) dando una espuma naranja. EM ($M+H^+$): calculado = 483,64, observado = 484,2.

Cloruro de (1R)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanaminio (**34-5**)

Se trató ({(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}amino)sulfoniumolato de *terc*-butilo (**34-4**) con HCl 4N en dioxano a temperatura ambiente durante 15 minutos. La mezcla de reacción se redujo bajo presión y se purificó mediante cromatografía en fase reversa (Waters Sunfire MSC18, acetonitrilo al 1%/ácido trifluoroacético al 0,1%/agua → acetonitrilo al 95%/ácido trifluoroacético al 0,1%/agua) y la conversión a sal de HCl (adición de solución saturada de HCl en acetato de etilo (~ 4N) y concentración) dio el compuesto del título como un sólido. EM ($M+H^+$): calculado = 379,47, observado = 380,2.

34-6

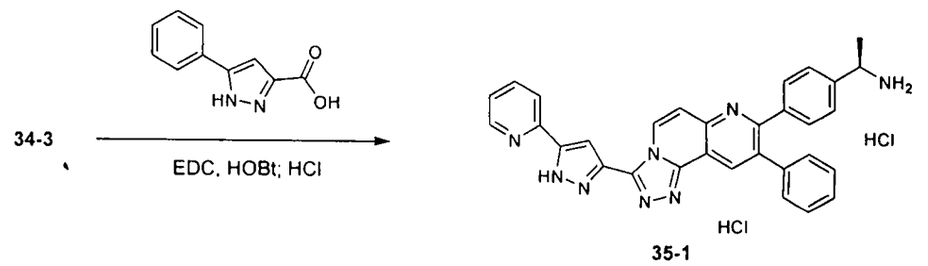



(1*R*)-1-[4-(9-fenil-3-propil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina

**(34-6)**

El compuesto del título se preparó de acuerdo con los procedimientos del Esquema 34; EM ($M+H^+$): calculado = 365,43, observado = 366,2. Se aisló compuesto **34-6** como una sal de HCl.

ESQUEMA 35



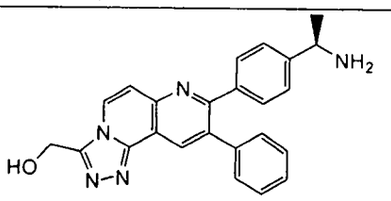
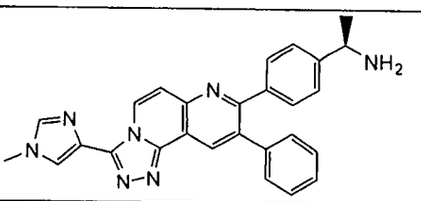

**35-1**

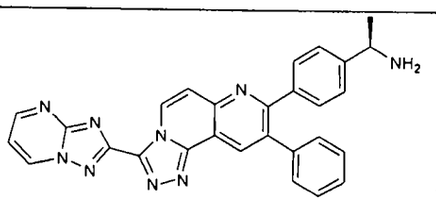
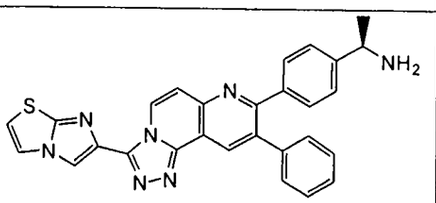
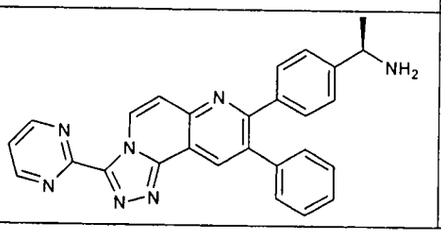
Diclorhidrato de (1*R*)-1-{4-[9-fenil-3-(5-piridin-2-il-1H-pirazol-3-il, 3-tiazol-5-il)[1,2,4]triazolo[3,4-f]-1,6- naftiridin-8-il]fenil}etanamina (**35-1**)

A ({(1*R*)-1-[4-(5-hidrazino-3-fenil-1,6-naftiridin-2-il)fenil]etil}amino)sulfoniumolato de *terc*-butilo (**34-3**, 0,20 g, 0,43 mmol), EDC (0,11 g, 0,57 mmol), HOBT anhidro (0,06 g, 0,39 mmol), DIPEA (0,17 ml, 0,96 mmol), y ácido 5-piridin-2-il-1H-pirazol-3-carboxílico (0,08 g, 0,43 mmol) se añadió DMF anhidro (2 ml) y se agitó a temperatura ambiente durante toda una noche. Se añadió HCl/éter (1 ml, 2N) a la mezcla de reacción y se agitó durante 20 minutos a temperatura ambiente, después se sometió a microondas a 100°C durante 30 min. El disolvente se eliminó bajo presión y se purificó mediante cromatografía en fase reversa (Waters Sunfire MSC18, acetonitrilo al 1%/ácido trifluoroacético al 0,1%/agua → acetonitrilo al 95%/ácido trifluoroacético al 0,1%/agua) y la conversión a sal de HCl (adición de solución saturada de HCl en acetato de etilo (~ 4N) y concentración) dio el compuesto del título como un sólido. EM ($M+H^+$): calculado = 508,58, observado = 509,1.

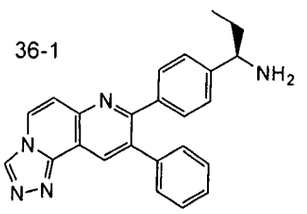
Los siguientes compuestos en la Tabla 13 se prepararon de acuerdo con el procedimiento de Esquema 35. Los compuestos en Tabla 13 se aislaron como sales de HCl.

Tabla 13

| Cmp | Estructura | Nombre | EM m/z (M+H) |
|---|---|---|---|
| **35-2** |  | (1R)-1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina | Observado: 396,0 |
| **35-3** |  | (1R)-1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8- | Observado: 445,9 |

| | | | |
|---|---|---|---|
| | | il]fenil}etanamina | |
| 35-4 |  | (1R)-1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina | Observado: 484,1 |
| 35-5 |  | (1R)-1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina | Observado: 488,0 |
| 35-6 |  | (1R)-1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina | Observado: 444,1 |

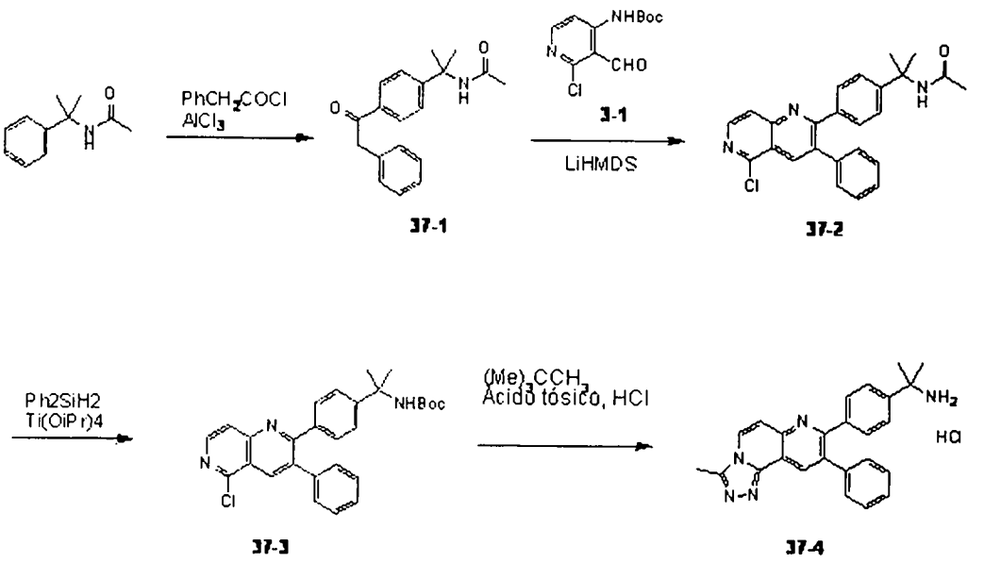
36-1



(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-1-amina (**36-1**)

El compuesto del título se preparó de acuerdo con los procedimientos de Esquema 34. EM ($M+H^+$): calculado = 379,47, observado = 380,2. El compuesto **36-1** se aisló como una sal de HCl.

ESQUEMA 37




2-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina (**37-4**)

*N*-{1-metil-1-[4-(fenilacetil)fenil]etil}acetamida (**37-1**)

Una solución de *N*-(1-metil-1-feniletil)acetamida (21,3 g, 121 mmol), cloruro de fenilacetilo (19,5 g, 126 mmol) y tricloruro de aluminio (19 g, 142 mmol) en cloruro de metileno (140 ml) se agitó durante toda una noche a temperatura ambiente bajo una atmósfera de nitrógeno. La reacción se vertió sobre hielo y se agitó bajo el la fusión de hielo, después las fases se separaron y la fase orgánica se lavó con bicarbonato de sodio saturado, salmuera, se secó sobre sulfato de magnesio, se filtró y se concentró. La purificación mediante cromatografía en gel de sílice dio el compuesto del título. EM ($M+H^+$): calculado = 295,38, observado = 296,1.

*N*-{1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]-1-metiletil}acetamida (**37-2**)

El compuesto del título se preparó a partir de **37-1** de acuerdo con el procedimiento del Esquema 3; EM ($M+H^+$): calculado = 415,91, observado = 416,1.

{1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]-1-metiletil}carbamato de *terc*-butilo (**37-3**)

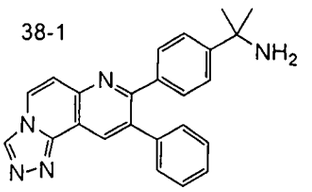
A una solución de *N*-{1-[4-(5-cloro-3-fenil-1,6-naftiridin-2-il)fenil]-1-metiletil}acetamida (**37-2**, 4,73 g, 11,4 mmol) en THF anhidro (120 ml) se añadió difenilsilano (10,5 ml, 56,9 mmol) e isopropóxido de titanio (16,6 ml, 56,9 mmol) a 40°C durante 1 hora. La mezcla de reacción se retiró del calor y se desactivó mediante adición de solución de bicarbonato saturada. Se añadió cloruro de metileno y se filtró a través de un lecho de celite y sulfato de magnesio. Se añadió dicarbonato de di-*terc*-butildicarbonato (3,08 g, 14,1 mmol) a la solución antes de someter a rotavapor para minimizar

volumen. Se añadieron cloruro de metileno anhidro (140 ml), dicarbonato de di-terc-butilo (4,1 g, 18,8 mmol), y TEA (4,0 ml, 28,7 mmol) y se agitaron durante toda una noche a temperatura ambiente. La mezcla de reacción se lavó con bicarbonato de sodio, salmuera, se secó sobre sulfato de magnesio, se filtró, y se concentró. Purificada mediante cromatografía en gel de sílice (EtOAc al 0-40%/hex sobre 30 min) dio el compuesto del título como una espuma blanca. EM ($M+H^+$): calculado = 473,99, observado = 474,1.

2-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina clorhidrato (**37-4**)

El compuesto del título se preparó a partir de **37-3** de acuerdo con los procedimientos del Esquema 5; EM (M+H+): calculado = 393,48, observado = 394,1.

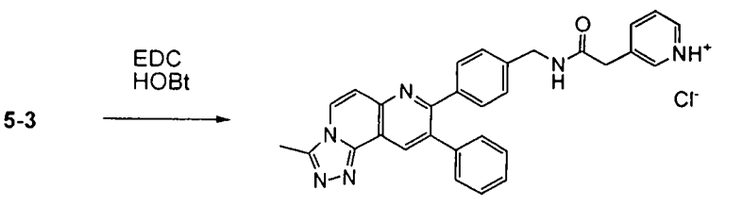
**38-1**



2-[4-(9-fenil-[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-3-amina (**38-1**)

El compuesto del título se preparó de acuerdo con los procedimientos del Esquema 37; EM ($M+H^+$): calculado = 421,51, observado = 422,3. Se aisló compuesto **38-1** como una sal de HCl.

ESQUEMA 39




**39-1**

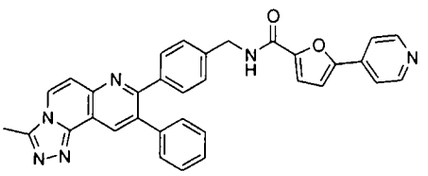
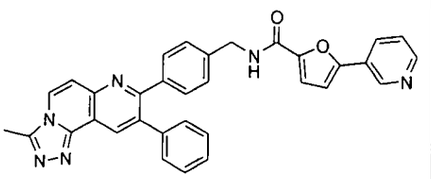
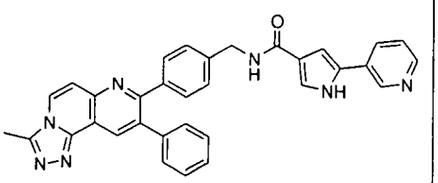
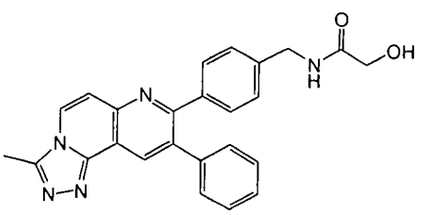
Cloruro 3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridinio (**39-1**)

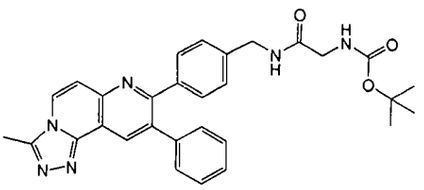
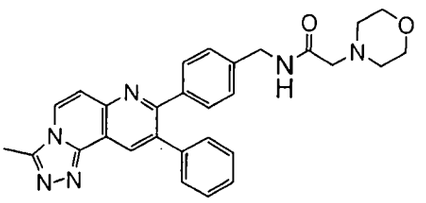
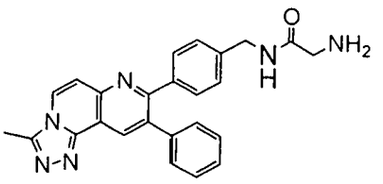
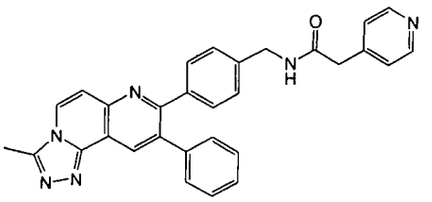
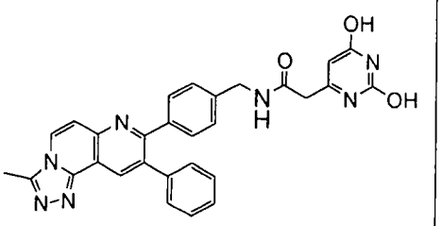
A clorhidrato de 1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]metanamina (**5-3**, 20 mg, 0,050 mmol) ), EDC (12 mg, 0,065 mmol), HOBT (10 mg, 0,0650 mmol), DIPEA (0,033 ml, 0,199 mmol), y clorhidrato de ácido piridin-3-ilacético (11 mg, 0,0650 mmol) se añadieron 0,6 ml de dimetilformamida anhidra. La mezcla de reacción se calentó después bajo irradiación de microondas a 100°C durante 5 minutos. Purificación de mezcla de reacción en bruto mediante cromatografía en fase reversa (Waters Sunfire MSC18, acetonitrilo al 1%/ácido trifluoroacético al 0,1%/agua → acetonitrilo al 95%/ácido trifluoroacético al 0,1%/agua) y conversión a sal de HCl

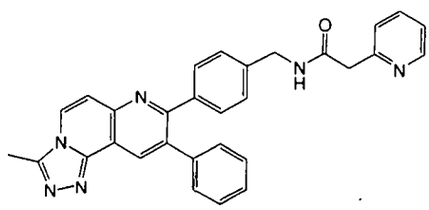
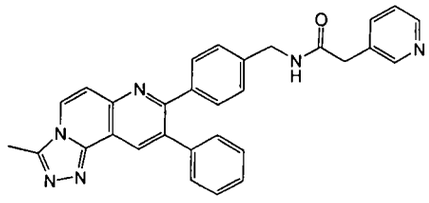
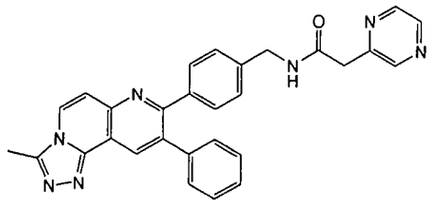
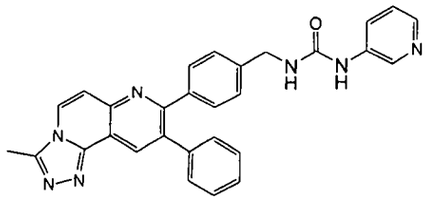
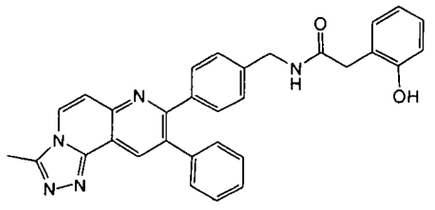
(adición de solución saturada de HCl en acetato de etilo (~ 4N) y concentración) dieron el compuesto del título como un sólido. HREM ($M+H^+$): calculado = 243,1079, observado = 243,1083.

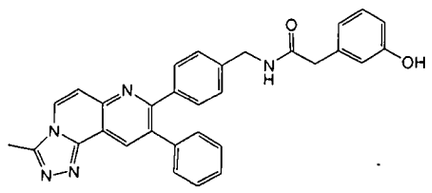
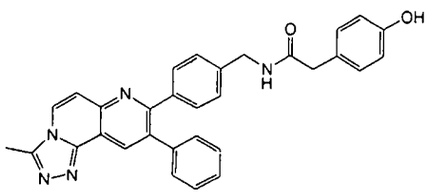
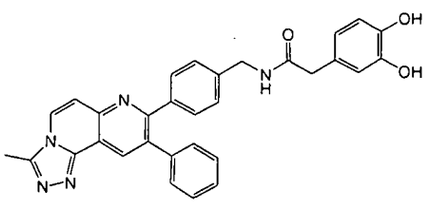
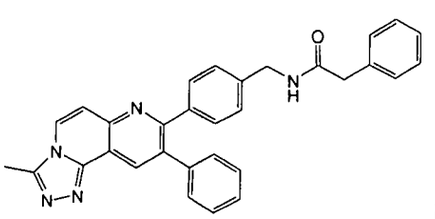
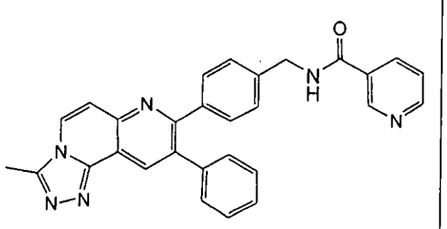
Los siguientes compuestos en Tabla 14 se prepararon a partir de la amina indicada (véase la explicación entre paréntesis de la columna de Cmp) de acuerdo con el procedimiento de Esquema 39.

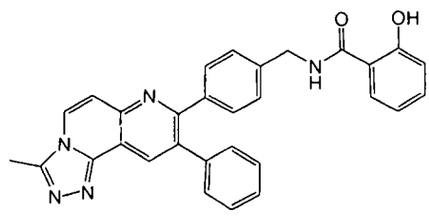
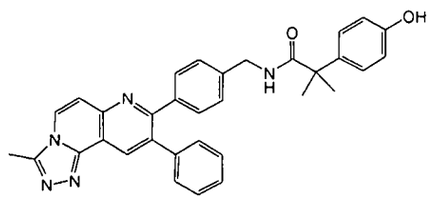
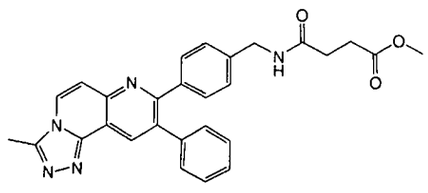
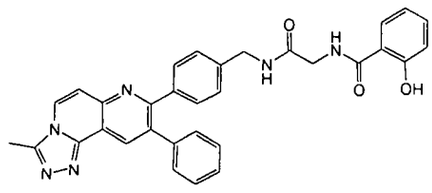
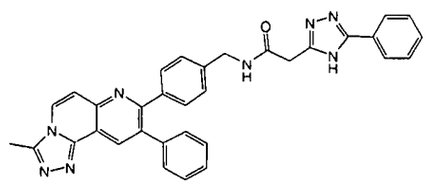
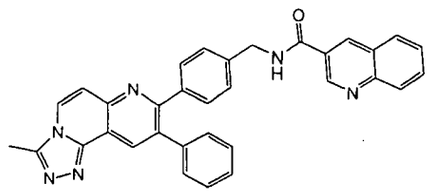
Tabla 14

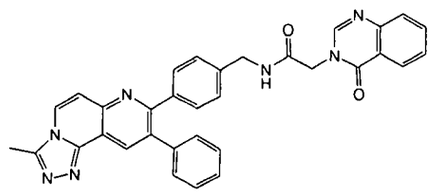
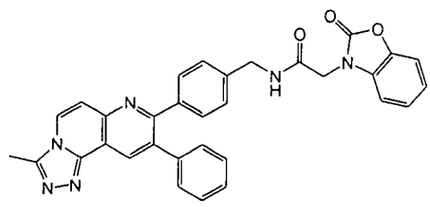
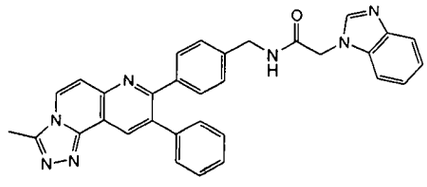
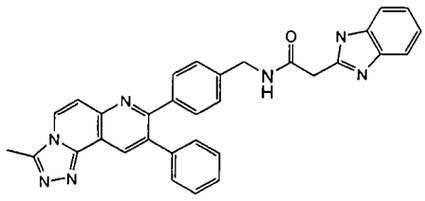
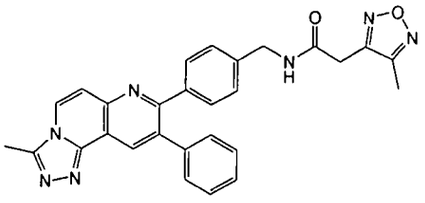
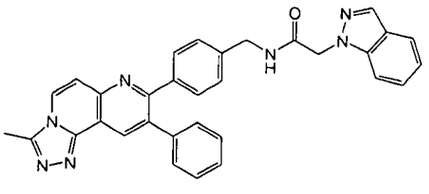
| Cmp (amina) | Estructura | Nombre | HREM m/z (M+H) |
|---|---|---|---|
| **39-2** (5-3) |  | *N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-4-il-2-furamida; aislada como una sal de TFA. | Calc.: 537,2034. Observado: 537,2027. |
| **39-3** (5-3) |  | *N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-2-furamida; aislada como una sal de HCl. | Calc.: 537,2034. Observado: 537,2023. |
| **39-4** (5-3) |  | *N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-1*H*-pirrol-3-carboxamida; aislada como una sal de HCl. | Calc.: 536,2194. Observado: 536,2218. |
| **39-5** (5-3) |  | 2-hidroxi-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida. | Calc.: 424,1768. Observado: 424,1767. |

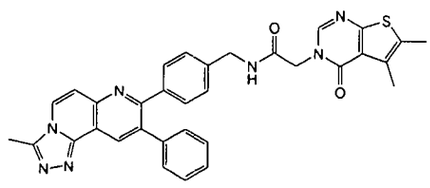
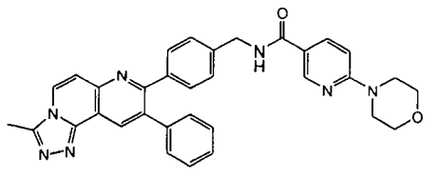
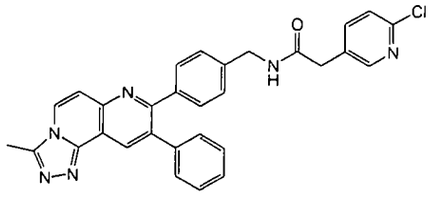
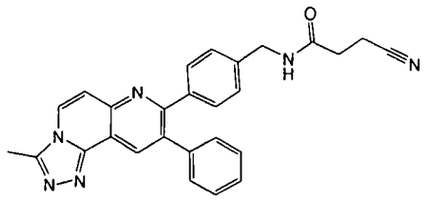
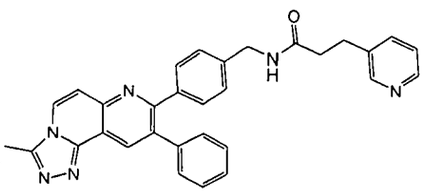
| | | | |
|---|---|---|---|
| **39-6**<br>(5-3) |  | (2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)carbamato de *terc*-butilo | Calc.: 523,2452.<br>Observado: 523,2444. |
| **39-7**<br>(5-3) |  | 4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)morfolina; aislada como una sal de HCl. | Calc.: 493,2347.<br>Observado: 493,2358. |
| **39-8**<br>(5-3) |  | 2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetanamina; aislada como una sal de HCl. | Calc.: 423,1928.<br>Observado: 423,1942. |
| **39-9**<br>(5-3) |  | 4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina; aislada como una sal de HCl. | Calc.: 485,2085.<br>Observado: 485,2120. |
| **39-10**<br>(5-3) |  | 2,4-dihidroxi-6-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)pirimidina; aislada como una sal de HCl. | Calc.: 518,1935.<br>Observado: 518,1960. |

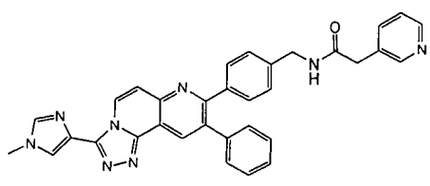
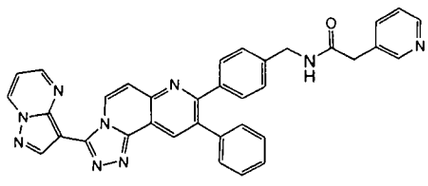
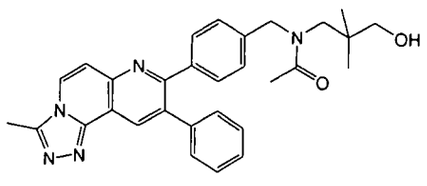
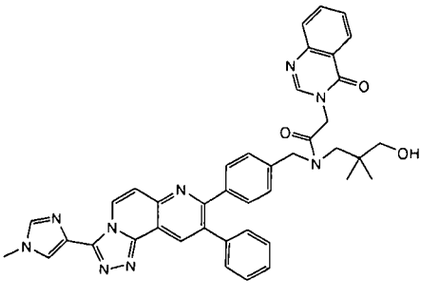
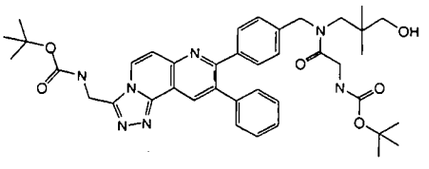
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| **39-11**<br>(5-3) |  | 2-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina; aislada como una sal de HCl. | Calc.: 485,2085.<br>Observado: 485,2118. |
| **39-12**<br>(5-3) |  | Cloruro 3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-oxoetil)piridinio. | Calc.: 243,1079.<br>Observado: 243,1083. |
| **39-13**<br>(5-3) |  | *N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-pirazin-2-ilacetamida | Calc.: 486,2037<br>Observado: 486,2044 |
| **39-14**<br>(5-3) |  | 3-metil-9-fenil-8-[4-({[(piridin-3-ilamino) carbonil]amino}metil)fenil][1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 486,2037.<br>Observado: 486,2056. |
| **39-15**<br>(5-3) |  | 2-(2-hidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida. | Calc.: 500,2081<br>Observado: 500,2087 |

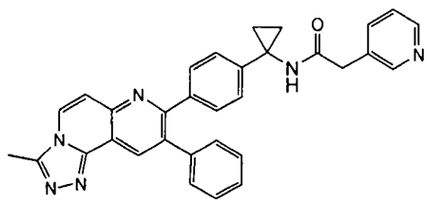
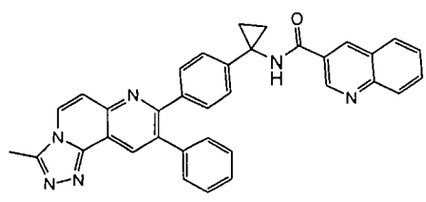
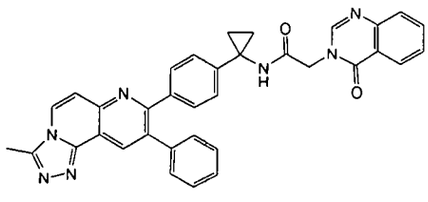
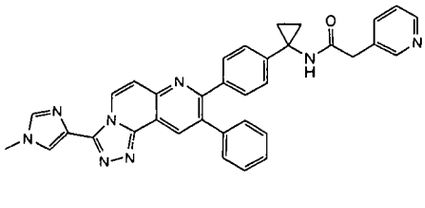
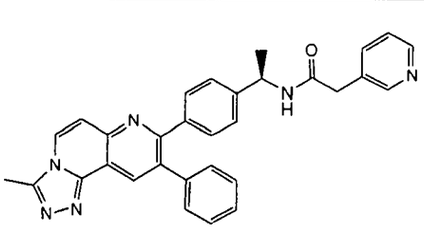
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|---|---|---|---|
| 39-16<br><br>(5-3) |  | 2-(3-hidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 500,2081.<br>Observado: 500,2086. |
| 39-17<br><br>(5-3) |  | 2-(4-hidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 500,2081.<br>Observado: 500,2085. |
| 39-18<br><br>(5-3) |  | 2-(3,4-dihidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 576,2030.<br>Observado: 576,2025. |
| 39-19<br><br>(5-3) |  | *N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-fenilacetamida. | Calc.: 484,2132.<br>Observado: 484,2161. |
| 39-20<br><br>(5-3) |  | 3-metil-9-fenil-8-(4-{[(piridin-3-ilcarbonil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 471,1928.<br>Observado: 471,1928. |

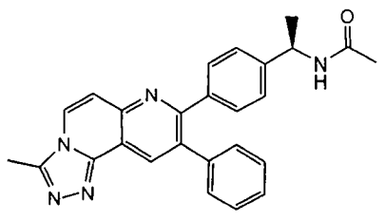
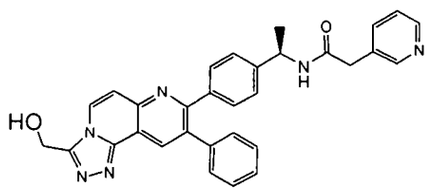
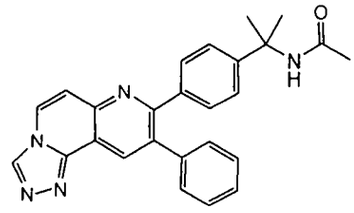
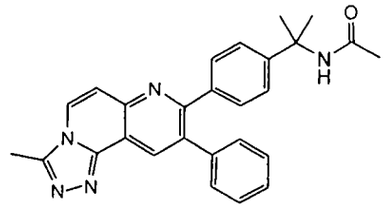
| | | | |
|---|---|---|---|
| **39-21**<br>(5-3) |  | 2-hidroxi-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]benzamida | Calc.: 486,1925. Observado: 486,1919. |
| **39-22**<br>(5-3) |  | 2-(4-hidroxifenil)-2-metil-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]propanamida. | Calc.: 528,2394. Observado: 528,2386. |
| **39-23**<br>(5-3) |  | 4-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-4-oxobutanoato de metilo. | Calc.: 480,2030. Observado: 480,2030. |
| **39-24**<br>(5-3) |  | 2-hidroxi-*N*-(2-{[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)benzamida. | Calc.: 543,2139. Observado: 543,2127. |
| **39-25**<br>(5-3) |  | *N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil] -2-(5-fenil-4*H*-1,2,4-triazol-3-il)acetamida. | Calc.: 551,2303 Observado: 551,2292. |
| **39-26**<br>(5-3) |  | 3-metil-9-fenil-8-(4-{[(quinolin-3-ilcarbonil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 521,2085. Observado: 521,2061. |

| | | | |
|---|---|---|---|
| **39-27**<br>**(5-3)** |  | *N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-(4-oxoquinazolin-3(4*H*)-il)acetamida. | Calc.: 552,2143.<br>Observado: 552,2126. |
| **39-28**<br>**(5-3)** |  | *N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-il)acetamida. | Calc.: 541,1983.<br>Observado: 541,1965. |
| **39-29**<br>**(5-3)** |  | 8-(4-{[(1*H*-benzimidazol-1-ilacetil)amino]metil}fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 524,2194.<br>Observado: 524,2199. |
| **39-30**<br>**(5-3)** |  | 8-(4-{[(1*H*-benzimidazol-2-ilacetil)amino]metil}fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 524,2194.<br>Observado: 524,2185. |
| **39-31**<br>**(5-3)** |  | 2-(4-metil-1,2,5-oxadiazol-3-il)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 440,1986.<br>Observado: 490,1976. |
| **39-32**<br>**(5-3)** |  | 2-(1*H*-indazol-1-il)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 524,2194.<br>Observado: 524,2171. |

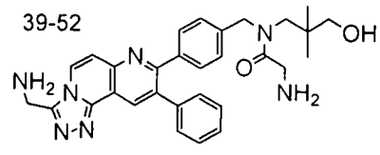
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| **39-33**<br>(5-3) |  | 2-(5,6-dimetil-4-oxotieno[2,3-*d*]pirimidin-3(4*H*)-il)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 586,2020.<br>Observado: 586,1993. |
| **39-34**<br>(5-3) |  | 3-metil-8-[4-({[(6-morfolin-4-ilpiridin-3-il)carbonil]amino}metil)fenil]-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina; aislado como una sal de HCl. | Calc.: 556,2456.<br>Observado: 556,2441. |
| **39-35**<br>(5-3) |  | 2-(6-cloropiridin-3-il)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 519,1695.<br>Observado: 519,1673. |
| **39-36**<br>(5-3) |  | 3-ciano-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)bencil]propanamida | Calc.: 447,1928.<br>Observado: 447,1921. |
| **39-37**<br>(5-3) |  | 3-metil-9-fenil-8-(4-{[(3-piridin-3-ilpropanoil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 499,2241.<br>Observado: 499,2244. |

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| **39-38**<br><br>**(16-44)** |  | 3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 551,2303.<br>Observado: 551,2326. |
| **39-39**<br><br>**(16-22)** |  | 9-fenil-3-pirazolo[1,5-*a*]pirimidin-3-il-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de HCl. | Calc.: 588,2255.<br>Observado: 588,2276. |
| **39-40**<br><br>**(13-10)** |  | *N*-(3-hidroxi-2,2-dimetilpropil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida. | Calc.: 494,2551.<br>Observado: 494,2557. |
| **39-41**<br><br>**(13-16)** |  | *N*-(3-hidroxi-2,2-dimetilpropil)-*N*-{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il] bencil}-2-(4-oxoquinazolin-3(4*H*)-il)acetamida. | LREM<br>(M+1)=<br>Observado: 704,3. |
| **39-42**<br><br>**(13-20)** |  | {2-[[4-(3-{[(*terc*-butoxicarbonil)amino]metil}-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil](3-hidroxi-2,2-dimetilpropil)amino]-2-oxoetil}carbamato de | Calc.: 724,3817<br>Observado: 724,3822. |

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|---|---|---|---|
| | | *terc*-butilo | |
| **39-43**<br>**(33-5)** |  | 3-metil-9-fenil-8-(4-{1-[(piridin-3-ilacetil)amino]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de TFA. | Calc.: 511,2241<br>Observado: 511,2264. |
| **39-44**<br>**(33-5)** |  | 3-metil-9-fenil-8-(4-{1-[(quinolin-3-ilcarbonil)amino]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de TFA. | Calc.: 547,2241.<br>Observado: 547,2225. |
| **39-45**<br>**(33-5)** |  | *N*-{1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropil}-2-(4-oxoquinazolin-3(4*H*)-il)acetamida. | Calc.: 578,2299.<br>Observado: 578,2276. |
| **39-46**<br>**(33-6)** |  | 3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{1-[(piridin-3-ilacetil)amino]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina; aislada como una sal de TFA. | Calc.: 577,2459<br>Observado: 577,2488. |
| **39-47**<br>**(34-5)** |  | *N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo [3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}-2-piridin-3-ilacetamida; aislada como una sal de TFA. | LREM<br>(M+1)=<br>Observado: 498,8. |

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| **39-48**<br><br>**(34-5)** |  | *N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]acetamida | LREM<br>(M+1)=<br>Observado: 422,2. |
| **39-49**<br><br>**(34-5)** |  | *N*-((1*R*)-1-{4-[3-(hidroximetil)l-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}etil)-2-piridin-3-ilacetamida; aislada como una sal de HCl. | LREM<br>(M+1)=<br>Observado: 514,8. |
| **39-50**<br><br>**(38)** |  | *N*-{1-metil-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) fenil]etil}acetamida. | LREM<br>(M+1)=<br>Observado: 422,3. |
| **39-51**<br><br>**(37-4)** |  | *N*-{1-metil-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) fenil]etil}acetamida. | LREM<br>(M+1)=<br>Observado: 435,8. |

39-52



2-[{4-[3-(amoniometil)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]bencil}(3-hidroxi-2,2-dimetilpropil)amino]-2-oxoetanamina (**39-52**)

El compuesto del título se preparó de acuerdo con los procedimientos de Esquema 27 a partir de 39-42; EM ($M+H^+$): calc.: 524,2769, observado: 524,2777. Se aisló compuesto **39-52** como una sal de HCl.

EJEMPLO 1

Clonación de las isoformas de de Akt humanas y ΔPH-Akt1

El vector pS2neo (depositado en la ATCC en el 3 de abril de 2001 como ATCC PTA-3253) se preparó como sigue: el vector pRmHA3 (preparado como se describe en *Nucl. Acid Res.* 16:1043-1061 (1988)) se cortó con BglII y se aisló un fragmento de 2734 pb. El vector pUChsneo (preparado como se describe en *EMBO J.* 4:167-171 (1985)) se cortó con BglII y se aisló una banda de 4029 pb. Estos fragmentos aislados se ligaron conjuntamente generando un vector llamado pS2neo-1. Este plásmido contiene un poliengarce entre un promotor de metalotionina y un sitio de adición de poli A de alcohol deshidrogenasa. También tiene un gen de resistencia neo dirigido por un promotor de choque térmico. El vector pS2neo-1 se cortó con Psp5II y BsiWI. Se sintetizaron dos oligonucleótidos complementarios y después se fusionaron (CTGCGGCCGC (SEQ.ID.N°.: 1) y GTACGCGGCCGCAG (SEQ.ID.N°.: 2)). El pS2neo-1 de corte y los oligonucleótidos fusionados se ligaron conjuntamente generando un segundo vector, pS2neo. En esta conversión se añadió un sitio NotI para añadir en la linearización antes de transfección en células S2.

El gen Akt1 humano se amplificó mediante PCR (Clontech) fuera de un cDNA de bazo humano (Clontech) usando el cebador 5': 5'CGCGAATTCAGATCTACCATGAGCGACGTGGCTATTGTG 3' (SEQ.ID.N°.: 3), y el cebador 3': 5'CGCTCTAGAGGATCCTCAGGCCGTGCTGCTGGC3' (SEQ.ID.N°.: 4). El cebador 5' incluyó un sitio EcoRI y BglII. El cebador 3' incluyó un sitio XbaI y BamHI para propósitos de clonación. El producto de PCR resultante se subclonó en pGEM3Z (Promega) como un fragmento EcoRI/Xba I. Para propósitos de expresión/purificación, se añadió una marca de T central de longitud total al extremo 5' del gen Akt1 usando cebador de PCR: 5'GTACGATGCTGAACGATATCTTCG 3' (SEQ.ID.N°.: 5). El producto de PCR resultante abarcaba un sitio 5' KpnI y un sitio 3' BamHI los cuales se usaron para subclonar el fragmento en fase con un vector de expresión de células de insecto que contiene marca de biotina, pS2neo.

Para la expresión de una versión eliminada de dominio de homología de plecstrina ( PH ) (Δaa 4-129, el cual incluye deleción de una porción de la región bisagra de Akt1) de Akt1, la mutagénesis de deleción de PCR se hizo usando el gen de Akt1 de longitud total en el vector de pS2neo como plantilla. La PCR se llevó a cabo en 2 etapas usando cebadores internos sobrelapantes (5'GAATACATGCCGATGGAAAGCGACGGGGCTGAAGAGATGGAGGTG 3' (SEQ.ID.N°.: 6), y 5'CCCCTCCATCTCTTCAGCCCCGTCGCTTTCCATCGGCATGTATTC 3' (SEQ.ID.N°.: 7)) los cuales abarcaban la deleción y los cebadores flanqueantes 5' y 3' los cuales abarcaban el sitio KpnI y la marca de T central en el extremo 5'. El producto de PCR final se digirió con KpnI y SmaI y se ligó dentro del vector de corte de KpnI/SmaI de Akt1 de longitud total de pS2neo, que reemplaza efectivamente el extremo 5' del clon con la versión eliminada.

El gen Akt3 humano se amplificó mediante PCR de cDNA del cerebro adulto (Clontech) usando el cebador de oligo aminoterminal:

5' GAATTCAGATCTACCATGAGCGATGTTACCATTGTG 3' (SEQ.ID.N°.: 8); y el cebador de oligo carboxiterminal :

5' TCTAGATCTTATTCTCGTCCACTTGCAGAG 3' (SEQ.ID.N°.: 9).

Estos cebadores incluyeron un sitio 5' EcoRI/BglII y un sitio 3' XbaI/BglII para propósitos de clonación. El producto de PCR resultante se clonó dentro de los sitios EcoRI y XbaI de pGEM4Z (Promega). Para propósitos de expresión/purificación, se añadió una marca de T central al extremo 5' del clon Akt3 de longitud total usando el cebador de PCR:

5'GGTACCATGGAATACATGCCGATGGAAAGCGATGTTACCATTGTGAAG 3' (SEQ.ID.N°.: 10).

El producto de PCR resultante abarcaba un sitio 5' KpnI el cual permitió clonado en fase con el vector de expresión de células de insecto conteniendo marca de biotina, pS2neo.

El gen Akt2 humano se amplificó mediante PCR de cDNA del timo humano (Clontech) usando el cebador de oligo aminoterminal:

5' AAGCTTAGATCTACCATGAATGAGGTGTCTGTC 3' (SEQ.ID.N°.: 11); y el cebador de oligo carboxiterminal: 5'GAATTCGGATCCTCACTCGCGGATGCTGGC 3' (SEQ.ID.N°.: 12). Estos cebadores incluyeron un sitio 5' HindIII/BglII y un sitio 3' EcoRI/BamHI para propósitos de clonación. El producto de PCR resultante se subclonó dentro de los sitios de HindIII/EcoRI de pGem3Z (Promega). Para propósitos de expresión/purificación, se añadió una marca de T central al extremo 5' del gen Akt2 de longitud total usando el cebador de PCR:

5'GGTACCATGGAATACATGCCGATGGAAAATGAGGTGTCTGTCATCAAAG 3' (SEQ.ID.N°.: 13). El producto de PCR resultante se subclonó dentro del vector de pS2neo como se describe anteriormente.

## EJEMPLO 2

### Expresión de las isoformas de de Akt humanas y ΔPH-Akt1

El DNA que contiene los genes Akt1, Akt2, Akt3 y ΔPH-Akt1 clonados en el vector de expresión pS2neo se purificó y usó para transfectar células de *Drosophila* S2 (ATCC) mediante el procedimiento de fosfato de calcio. Se seleccionaron reservas de células resistentes a antibióticos (G418, 500 μg/ml). La célula se expandió a volumen de 1,0 l (~7,0 x $10^6$ /ml), se añadieron biotiona y $CuSO_4$ a una concentración final de 50 μM y 50 mM respectivamente. Las células se cultivaron durante 72 horas a 27°C y se recogieron mediante centrifugación. El extracto celular se enfrió a –70°C hasta que se necesitó.

## EJEMPLO 3

### Purificación de las isoformas de de Akt humanas y ΔPH-Akt1

El extracto celular de un litro de células S2, descritas en el Ejemplo 2, se lisó mediante sonicación con 50 mls de CHAPS al 1% en tampón A: (Tris 50mM pH 7,4, EDTA 1mM, EGTA 1mM, AEBSF 0,2 mM, benzamidina a 10 μg/ml, 5μg/ml de leupeptina, aprotinina y pepstatina cada una, glicerol al 10% y DTT 1 mM). La fracción soluble se purificó en una columna de flujo rápido de Sefarosa de Proteína G (Pharmacia) cargada con anticuerpo monoclonal anti-T central a 9 mg/ml y eluyó con péptido EYMPPME 75 μM (SEQ.ID.N°.: 14) en tampón A que contiene glicerol al 25%. Se

almacenaron las fracciones que contienen Akt/PKB y la pureza de la proteína se evaluó mediante SDS-PAGE. La proteína purificada se cuantificó usando un protocolo de Bradford estándar. La proteína purificada se congeló de forma ultrarrápida en nitrógeno líquido y se almacenó a -70°C.

Las deleciones del dominio de homología de Akt y plecstrina de Akt purificadas a partir de células S2 requirieron activación. Se activaron las deleciones del dominio de homología de Akt y plecstrina de Akt (Alessi y col. *Current Biology* 7:261-269) en una reacción que contenía PDK1 10 nM (Upstate Biotechnology, Inc.), vesículas lipídicas (fosfatidilinositol-3,4,5-trisfosfato– Metreya, Inc. 10 µM, fosfatidilcolina 100 µM y fosfatidilserina – Avanti Polar lipids, Inc. 100 µM ) y tampón de activación (Tris 50 mM pH 7,4, DTT 1,0 mM, EGTA 0,1 mM, Microcistina–LR 1,0 µM, ATP 0,1 mM, $MgCl_2$ 10 mM, BSA a 333 µg/ml BSA y EDTA 0,1 mM ). La reacción se incubó a 22°C durante 4 horas. Las alícuotas se congelaron de forma ultrarrápida en nitrógeno líquido.

EJEMPLO 4

Ensayos de Kinasa Akt

Las construcciones de deleción de dominio de homología de isoformas de Akt y plecstrina activada se ensayaron utilizando un sustrato peptídico biotinilado derivado de GSK. La extensión de fosforilación de péptidos se determinó mediante Fluorescencia Resuelta de Tiempo Homogéneo (HTRF) usando un anticuerpo monoclonal acoplado a quelato de lantánido específico (Lance) para el fosfopéptido en combinación con una aloficocianina ligada a estreptavidina (SA-APC) la cual se une al resto de biotina en el péptido. Cuando el Lance y APC están en proximidad (es decir unidos a la misma molécula de fosfopéptido), tiene lugar una transferencia de energía no radiactiva del Lance al APC, seguida por emisión de luz de APC a 665 nm.

Materiales requeridos para el ensayo:

A. Construcción eliminada de dominio de homología de isozima de Akt o plecstrina activada.

B. Sustrato de péptido Akt: GSK3α (S21) Péptido #3928 de biotina-GGRARTSSFAEPG (SEQ.ID.N°.:15), Recursos Macromoleculares.

C. Anticuerpo monoclonal marcado con Lance anti-fosfoGSK3α (Cell Signaling Technology, clon # 27).

D. SA-APC (catálogo Prozyme n°. PJ25S lote # 896067).

E. Placas de Microtitulación de Fondo Microfluor®B U (Dynex Technologies, n°. de catálogo 7205).

F. Analizador de Microplaca de HTFR®, Packard Instrument Company.

G. Cóctel Inhibidor de Proteasa 100 X (PIC): benzamidina 1 mg/ml, pepstatina a 0,5 mg/ml, leupeptina a 0,5 mg/ml, aprotinina a 0,5 mg/ml.

H. Tampón de Ensayo 10X: HEPES 500 mM, pH 7,5, PEG al 1%, EDTA 1 mM, EGTA 1 mM, BSA al 1%, 9-glicerolfosfato 20 mM.

I. Tampón de Desactivación: HEPES 50 mM pH 7,3, EDTA 16,6 mM, BSA al 0,1%, Tritón X-100 al 0,1%, clon # 27 de anticuerpo monoclonal marcado con Lance 0,17 nM, SA-APC a 0,0067 mg/ml.

J. Solución de trabajo ATP/$MgCl_2$: tampón de ensayo 1X , DTT 1 mM, PIC 1X, KCl 125 mM, glicerol al 5%, $MgCl_2$ 25 mM, ATP 375 TM.

K. Solución de trabajo enzimática: tampón de ensayo 1X, DTT 1 mM, PIC 1X, glicerol al 5%, Akt activo. Las concentraciones de enzima finales se seleccionaron tal que el ensayo estuvo en un intervalo de respuesta lineal.

L. Solución de trabajo de péptidos: tampón de ensayo 1X, DTT 1 mM, PIC 1X, glicerol al 5%, péptido # 3928 biotinilado de GSK3 2 TM.

Las reacciones se ensamblan añadiendo 16 Tl de la solución de trabajo de ATP/$MgCl_2$ a los pocillos apropiados de una placa de microvaloración de 96 pocillos. Se añadió inhibidor o vehículo (1,0 Tl ) seguido por 10 Tl de solución de trabajo de péptidos. La reacción se comenzó añadiendo 13 Tl de la solución de trabajo de enzimas y mezclando. La reacción se dejó seguir durante 50 minutos y después se detuvo mediante la adición de 60 Tl de tampón de desactivación de HTRF. Las reacciones detenidas se incubaron a temperatura ambiente durante al menos 30 minutos y después se leyeron en el instrumento de Discovery.

Procedimiento para Ensayo de Placa Ultrarrápido de Estreptavidina:

Etapa 1:

Se añadió una solución de 1 µl del compuesto prueba en DMSO al 100% a 20 µl de solución de sustrato 2X (péptido GSK3 20 uM, ATP 300 µM, $MgCl_2$ 20 mM, [$\gamma^{33}$P] ATP a 20µ Ci/ml , tampón de ensayo 1X , glicerol al 5%, DT 1 mM, PIC 1X, BSA al 0,1% y KCl 100 mM KCl). Las reacciones de fosforilación se iniciaron añadiendo 19 µl de solución enzimática 2X (Akt/PKB activa 6,4 nM, Tampón de Ensayo 1X, glicerol al 5%, DTT 1 mM, PIC 1X y BSA al 0,1%). Las reacciones se incubaron después a temperatura ambiente durante 45 minutos.

Etapa 2:

La reacción se detuvo añadiendo 170 µl de EDTA 125 mM. Se transfirieron 200 µl de reacción detenida a una Flashplate® PLUS de Estreptavidina (NEN Life Sciences, n°. de catálog.: SMP103). La placa se incubó durante ≥10 minutos a temperatura ambiente en un agitador de placa. Los contenidos de cada pocillo se aspiraron, y los pocillos se aclararon 2 veces con 200 µl de TBS por pocillo. Los pocillos se lavaron después 3 veces durante 5 minutos con 200 µl de TBS por pocillo con las placas incubadas a temperatura ambiente en un agitador de plataforma durante las etapas de lavado.

Las placas se recubrieron con cinta selladora y se contaron usando la Packard TopCount con los ajustes apropiados para contar [$^{33}$P] en Flashplates.

Procedimiento para Ensayo de Placa de Filtro de Estreptavidina:

Etapa 1:

Las reacciones enzimáticas se llevaron a cabo como se describen en la Etapa 1 del Ensayo de Placa Ultrarrápido de Estreptavidina anteriormente.

Etapa 2:

La reacción se detuvo añadiendo 20 µl de Clorhidrato de Guanidina 7,5 M. Se transfirieron 50 µl de la reacción detenida a la placa de filtro de Estreptavidina (Placa de Captura de Biotina SAM$^{2TM}$ , Promega, nº. de catálogo V7542) y la reacción se incubó en el filtro durante 1-2 minutos antes de aplicar vacío.

La placa se lavó después usando un colector de vacío como sigue: 1) 4 x 200 µl/pocillo de NaCl 2M; 2) 6 x 200 µl/pocillo de NaCl 2M con $H_3PO_4$ al 1%; 3) 2 x 200 µl/pocillo de di$H_2O$; y 4) 2 x 100 µl/pocillo de etanol al 95%. Las membranas se dejaron después secar al aire completamente antes de añadir producto centelleante.

El fondo de la placa se selló con cinta de apoyo blanca, se añadieron 30 µl/pocillo de Microscint 20 (Packard Instruments, nº. de catálogo 6013621). La parte superior de la placa se selló con cinta de sellado transparente, y la placa se contó después usando el Packard TopCount con los ajustes apropiados para [$^{33}$P] con centelleante líquido.

Procedimiento para Ensayo de Placa de Filtro de Fosfocelulosa:

Etapa 1:

Las reacciones enzimáticas se llevaron a cabo como se describe en la Etapa 1 del Ensayo de Placa Ultrarrápido de Estreptavidina (anterior) utilizando KKGGRARTSSFAEPG (SEQ.ID.Nº.: 16) como el sustrato en lugar de biotina-GGRARTSSFAEPG.

Etapa 2:

La reacción se detuvo añadiendo 20 µl de $H_3PO_4$ 0,75%. Se transfirieron 50 µl de reacción detenida a la placa de filtro (UNIFILTER™, Intercambiador de Cationes Fuerte P81 de Whatman, Placas de 96 Pocillos de Poliestireno Blanco, Polyfiltronics, nº. de catálogo 7700-3312) y la reacción se incubó en el filtro durante 1-2 minutos antes de aplicar vacío.

La placa se lavó después usando un colector de vacío como sigue: 1) 9 x 200 µl/pocillo de $H_3PO_4$ al 0,75% y 2) 2 x 200 µl/pocillo de di$H_2O$. El fondo de la placa se selló con cinta de apoyo blanca, después se añadieron 30 µl/pocillo de Microscint 20. La parte superior de la placa se selló con cinta de sellado transparente, y la placa se contó usando el Packard TopCount con los ajustes apropiados para [$^{33}$P] y centelleante líquido.

Ensayo de PKA:

Cada ensayo de PKA individual consta de los siguientes componentes:

A. tampón de ensayo PKA 5X (Tris 200 mM pH 7,5, $MgCl_2$ 100 mM, 9-mercaptoetanol 5mM, EDTA 0,5 mM)

B. reserva de 50 µM de Kemptide (Sigma) diluido en agua

C. $^{33}$P-ATP preparado diluyendo 1,0 µl $^{33}$P-ATP [10 mCi/ml] dentro de 200 Tl de una reserva 50 µM de ATP no marcado

D. 10 µl de una reserva de 70 nM de subunidad catalítica de PKA (catálogo UBI # 14-114) diluida en BSA 0,5 mg/ml

E. Solución de trabajo de PKA/Kemptide: volúmenes iguales de tampón de ensayo de PKA 5X, solución de Kemptide y subunidad catalítica de PKA.

La reacción se llevó a cabo en una placa de ensayo de 96 pocillos profundos. El inhibidor o vehículo (10 Tl) se añade a 10 Tl de una solución de $^{33}$P-ATP. La reacción se inició añadiendo 30 Tl de la solución de trabajo de PKA/Kemptide a cada pocillo. Las reacciones se mezclaron e incubaron a temperatura ambiente durante 20 min. Las reacciones se pararon añadiendo 50 Tl de EDTA 100 mM EDTA y pirofosfato de sodio a 100 mM y mezclando.

El producto de reacción enzimática (Kemptide fosforilado) se recogió en placas de filtro de 96 pocillos de fosfocelulosa p81 (Millipore). Para preparar la placa, cada pocillo de una placa de filtro p81 se cargó con ácido fosfórico 75 mM. Los pocillos se vaciaron a través de filtro aplicando un vacío al fondo de la placa. Se añadió a cada pocillo ácido fosfórico (75 mM, 170 µl). Una alícuota de 30 µl de cada reacción de PKA detenida se añadió a los pocillos correspondientes en la placa de filtro que contienen el ácido fosfórico. El péptido se atrapó en el filtro tras la aplicación de un vacío y los filtros se lavaron 5 veces con ácido fosfórico 75 mM. Después del lavado final, los filtros se dejaron secar al aire. Se añadió fluido de centelleo (30 µl) a cada pocillo y los filtros se contaron en un TopCount (Packard).

Ensayo de PKC:

Cada ensayo de PKC consta de los siguientes componentes:

A. tampón de coactivación de PCK 10X: EGTA 2,5 mM, $CaCl_2$ 4 mM.

B. tampón de activación de PKC 5X: fosfatidilserina 1,6 mg/ml, diacilglicerol 0,16 mg/ml, Tris 100 mM pH 7,5, $MgCl_2$ 50 mM, 9-mercaptoetanol 5 mM.

C. $^{33}$P-ATP preparado diluyendo 1,0 µl de $^{33}$P-ATP [10 mCi/ml] dentro de 200 µl de una reserva 100 µM de ATP no marcado.

D. proteína básica de Mielina (350 µg/ml, UBI) diluida en agua.

E. PKC (50 ng/ml, catálogo UBI # 14-115) diluido en BSA a 0,5 mg/ml.

F. solución de trabajo de PKC/Proteína Básica de Mielina: preparada mezclando 5 volúmenes de cada uno de tampón de coactivación de PKC y Proteína Básica de Mielina con 10 volúmenes de cada uno de tampón de activación de PCK y PKC.

Los ensayos se ensamblaron en placas de ensayo de 96 pocillos profundos. Se añadió inhibidor o vehículo (10 Tl) a 5,0 ul de $^{33}$P-ATP. Se iniciaron las reacciones con la adición de la solución de trabajo de PKC/Proteína Básica de Mielina y mezclando. Las reacciones se incubaron a 30°C durante 20 min. Las reacciones se pararon añadiendo 50 Tl de EDTA 100 mM y pirofosfato de sodio 100 mM y mezclando. La Proteína Básica de Mielina Fosforilada se recogió en membranas de PVDF en placas de filtro de 96 pocillos y se cuantificó mediante cuenta de centelleo.

Los compuestos de la invención actual descritos en los Esquemas y Tablas se probaron en el ensayo descrito anteriormente y se encontraron teniendo $CI_{50}$ de $\leq$ 50 μM contra una o más de Akt1, Akt2 y Akt3.

EJEMPLO 5

Ensayos basados en Células para Determinar Inhibición de Akt/PKB

Las células (por ejemplo LnCaP o una línea celular tumoral $PTEN^{(-/-)}$ con Akt/PKB activada) se plaquearon en placas 100 mM. Cuando las células fueron aproximadamente confluyentes al 70 u 80%, las células se realimentaron con 5 ml de medios recientes y se añadió el compuesto de prueba en solución. Los controles incluyeron células no tratadas, células tratadas con vehículo y células tratadas bien con LY294002 (Sigma) o bien con wortmanina (Sigma) a 20 μM o 200 nM, respectivamente. Las células se incubaron durante 2, 4 ó 6 horas, y los medios se eliminaron, las células se lavaron con PBS, se rasparon y se transfirieron a un tubo de centrífuga. Se centrifugaron y volvieron a lavar con PBS. Finalmente, el sedimento celular se resuspendió en tampón de lisis (Tris 20 mM pH 8, NaCl 140 mM, EDTA 2 mM, Tritón al 1%, Pirofosfato de sodio 1 mM, fosfato de 9-glicerol 10 mM, NaF 10 mM, 0,5 mm de $NaVO_4$, Microsistina 1 μM , y Cóctel Inhibidor de Proteasa 1x), se situó en hielo durante 15 minutos y se removió suavemente lisando las células. El lisado se hizo girar en una ultracentrífuga de tablero Beckman a 100.000 x g a 4°C durante 20 min. La proteína del sobrenadante se cuantificó mediante un protocolo estándar de Bradford (BioRad) y se almacenó a –70°C hasta que se necesitó.

Las proteínas se inmunoprecipitaron (IP) a partir de lisados aclarados como sigue: para Akt1/PKBl, se mezclaron los lisados con sc-7126 (D-17) de Santa Cruz en NETN (100 mM NaCl, Tris 20 mM pH 8,0, EDTA 1 mM, NP-40 al 0,5%) y se añadió Agarosa de Proteína A/G (Santa Cruz sc-2003). Para Akt2/PKBϑ, se mezclaron los lisados en NETN con agarosa anti-Akt2 (Upstate Biotechnology #16-174) y para Akt3/PKBK, se mezclaron los lisados en NETN con agarosa anti-Akt3 (Upstate Biotechnology #16-175). Los IP se incubaron durante toda una noche a 4°C, se lavaron y se separaron mediante SDS-PAGE.

Las pruebas de bandas de Western se usaron para analizar Akt total, pThr308 Akt1, pSer473 Akt1, y los sitios de fosforilación correspondientes en Akt2 y Akt3, y dianas que actúan después usando anticuerpos específicos (Cell Signaling Technology): anti-Akt total ( nº. de catálogo 9272), Anti-Fosfo Akt Serina 473 ( nº. de catálogo 9271), y Anti-Fosfo Akt Treonina 308 ( nº. de catálog 9275). Después de incubar con el anticuerpo primario apropiado diluido en PBS + leche desnatada en polvo al 0,5% (NFDM) a 4 °C durante toda una noche, las bandas se lavaron, se incubaron con anticuerpo secundario marcado con peroxidasa de rábano picante (HRP) en PBS + NFDM al 0,5% durante 1 hora a temperatura ambiente. Se detectaron proteínas con reactivos de ECL (Amersham/Pharmacia Biotech RPN2134).

EJEMPLO 6

Activación de Akt Estimulada por Heregulina

Las células MCF7 (una línea celular de cáncer de mama humano que es $PTEN^{+/+}$) se

plaquearon a 1 x $10^6$ células por placa de 100 mM. Cuando las células fueron confluyentes al 70 – 80%, se realimentaron con 5 ml de medios libres de suero y se incubaron durante toda una noche. La mañana siguiente se añadió compuesto y las células se incubaron durante 1-2 horas, tiempo después del cual se añadió heregulina (para inducir la activación de Akt) durante 30 minutos y las células se analizaron como se describe anteriormente.

EJEMPLO 7

Inhibición de Crecimiento Tumoral

La eficacia in vivo de un inhibidor del crecimiento de células cancerosas se puede confirmar mediante varios protocolos bien conocidos en la técnica.

Las líneas celulares tumorales humanas las cuales presentan una desrregulación de la ruta de PI3K (tales como LnCaP, PC3, C33a, OVCAR-3, MDA-MB-468, A2780 o similares) se inyectaron subcutáneamente dentro del flanco izquierdo de ratones desnudos hembra de 6-10 semanas de edad (también ratones machos [de edad 10-14 semanas] se usaron para xenotransplantes de tumores de próstata [LnCaP y PC3]) (Harlan) en día 0. Los ratones se asignaron aleatoriamente a un grupo de tratamiento con vehículo, compuesto o combinación. La administración subcutánea diaria comienza en día 1 y continúa durante la duración del experimento. Alternativamente, el compuesto de prueba del inhibidor se puede administrar mediante una bomba de infusión continua. El compuesto, la combinación de compuestos o el vehículo se administran en un volumen total de 0,2 ml. Los tumores se escinden y pesan cuando todos los animales tratados con vehículo presentaron lesiones de 0,5-1,0 cm de diámetro, típicamente 4-5,5 semanas después de que se inyectaran las células. Se calcula el peso promedio de los tumores en cada grupo de tratamiento para cada línea celular.

EJEMPLO 8

Ensayo de Manchas Multiplex

Este procedimiento describe un inmunoensayo de sandwich usado para detectar proteínas fosforiladas múltiples en el mismo pocillo de una placa de formato de 96 pocillos. Los lisados celulares se incubaron en placas de 96 pocillos en los cuales se sitúan anticuerpos de captura diferentes en manchas inconfundibles espacialmente en el mismo pocillo. Se añadieron los anticuerpos policlonales de conejos específicos de fosforilación y el complejo se detectó mediante un anticuerpo anticonejo marcado con una marca electroquimioluminescente.

Placas LNCaP de 96-Pocillos +/- compuestos:

Centrifugar en Beckman J6 a 1200 rpm 10 minutos, aspirar los medios. Añadir 50 µl/pocillo: TBS (Pierce #28376-Tris 20 mM pH 7,5, NaCl 150 mM) + Tritón X-100 al 1% + Inhibidores de Proteasa y Fosfatasa. Envolver en envoltura de plástico, situar en congelador a -70°C hasta que se congelan completamente. Bloquear Placas Multiplex (Meso Scale Discovery, Gaithersburg, MD) con Bloqueador A al 3% en Tampón de Lavado de Tris 1X, 150 µl/pocillo. Cubrir con sellador de placa, incubar en agitador de Micromix 2 horas a temperatura ambiente (mínimo). Lavar con RCM 51 1X (TTBS). Descongelar las placas de lisado celular en hielo, añadir 40 µl de lisado/pocillo dentro de placas

bloqueadas. Cubrir con sellador de placa, incubar en mezclador de Micromix a 4°C O/N, lavar con RCM 51 1X. Diluir Anticuerpos Secundarios en Bloqueador A al 1% en Tampón de Lavado de Tris 1X: Antifosfo AKT (T308), Antifosfo Tuberina (T1462), solos o en combinación. Añadir 25 µl/pocillo, cubrir con sellador de placa, incubar en agitador de Micromix a temperatura ambiente 3 horas. Lavar con RCM 51 1X. Diluir Ru-GAR en Bloqueador A al 1% en Tampón de Lavado de Tris 1X. Añadir 25 µl/pocillo, cubrir con sellador de placa, incubar en agitador de Micromix a temperatura ambiente 1 hora. Lavar con RCM 51 1X. Diluir Tampón de Lectura T 4X a 1X con agua, añadir 200 µl de Tampón de Lectura diluido/pocillo.

Leer en Sector 6000 Imager.

Inhibidores de Proteasa y Fosfatasa:

Microcistina-LR, Calbiochem # 475815 a una concentración final 1 µM (reserva = 500 µM).

Calbiochem # 524624, Ajuste I 100X

Calbiochem # 524625, Ajuste II 100X

Calbiochem # 539134, Ajuste III 100X

Anti Fosfo AKT (T308):

Cell Signaling Technologies # 9275

Anti FosFo Tuberina (T1462):

Purificado por Afinidad de Covance (Conejos MS 2731/2732)

Ru-GAR = Antirratón de Cabra Rutenilado

Tampón de Lavado de Tris 10X, Bloqueador A y Tampón de Lectura T 4X

RCM 51 10X (TTBS 10X, RCM 51)

1X = Tris 20mM pH 7,5, NaCl 140 mM, Tween-20 al 0,1%

## EJEMPLO 9

Ensayo Basado en Células (In vivo)

Este procedimiento describe un ensayo de actividad basado en células (in vivo) para la serina/treonina kinasa de Akt. La Akt activada endógena es capaz de fosforilar un sustrato de Akt específico (GSK3β) el cual está biotinilado. La detección se lleva a cabo mediante Fluorescencia Resuelta de Tiempo Homogéneo (HTRF) usando un anticuerpo acoplado a kriptato de europio [Eu(K)] específico para el fosfopéptido y fluoróforo XL665 ligado a estreptavidina el cual se unirá al resto de biotina en el péptido. Cuando el [Eu(K)] y XL665 están en proximidad (es decir unidos a la misma molécula de fosfopéptido) tiene lugar una transferencia de energía no radiactiva del [Eu(K)] al XL665, seguida por emisión de luz de XL665 a 665 nm.

El ensayo se puede usar para detectar inhibidores de todas las tres isozimas de Akt (Akt1, Akt2, y Akt3) a partir de múltiples especies diferentes si existen anticuerpos específicos para cada una.

MATERIALES Y REACTIVOS

A. Placas de 96 pocillos de Fondo Plano de Microvaloración de Cultivos Celulares, Corning Costar, nº. de catálogo 3598

B. Placas de 96 pocillos Recubiertas de Proteína A Reacti-Bind, Pierce, nº. de catálogo 15130.

C. Placas de 96 pocillos Recubiertas de Proteína G Reacti-Bind, Pierce, nº. de catálogo 15131.

D. Micromix 5 Shaker.

E. Placas de Microtitulación de Fondo Microfluor®B U, Dynex Technologies, nº. de catálogo 7205.

F. Lavador de Placas de 96 Pocillos, Bio-Tek Instruments, nº. de catálogo EL 404.

G. Analizador de Microplaca de HTFR®, Packard Instrument Company.

SOLUCIONES TAMPÓN

A. Tampón de Lisis Celular de Kinasa IP: TBS 1X; Tween 20 al 0,2%; Cóctel Inhibidor de Proteasas III 1X (la Reserva es 100X, Calbiochem, 539134); Cóctel Inhibidor de Fosfatasas I 1X (la Reserva es 100X, Calbiochem, 524624); y Cóctel Inhibidor de Fosfatasas II 1X (la Reserva es 100X, Calbiochem, 524625).

B. Tampón de Ensayo 10X: Hepes 500 mM pH 7,5; PEG 1%; EDTA 1 mM; EGTA 1 mM; y β-glicerofosfato 20 mM.

C. Tampón de Ensayo de Kinasa IP: Tampón de Ensayo 1X; KCl 50 mM; ATP 150 µM; $MgCl_2$ 10 mM; Glicerol al 5%; DTT 1 mM; 1 Comprimido de Cóctel Inhibidor de Proteasa por 50 ml de Tampón de Ensayo; y BSA al 0,1%.

D. Solución de Sustrato GSK3β: Tampón de Ensayo de Kinasa IP; y péptido GSK3β Biotinilado 500 nM.

E. Tampón de Lance: Hepes 50 mM pH 7,5; BSA 0,1%; y Tritón X-100 al 0,1%.

F. Tampón de Parada de Lance: Tampón de Lance; y EDTA 33,3 mM .

G. Tampón de Detección de Lance: Tampón de Lance; SA-APC al 13,3 µg/ml ; y EuK Ab a-fosfo (Ser-21) GSK3ß 0,665 nM.

Ensayo de Kinasa Akt de Inmunoprecipitación Multi-Etapa

Día 1

A. Etapa de Sembrar células C33a: 60.000 células C33a de placa/pocillo en placa de microvaloración de 96 pocillos.

B. Incubar células durante toda una noche a 37°C.

Día 2

D. Etapa de Adición de Compuesto: añadir compuestos en medios frescos (alfa-MEM/FBS al 10%, temperatura ambiente) a placa de 96 pocillos de lo anterior e incubar durante 5 horas en incubador de cultivo de tejido.

E. Etapa de Lisis Celular: aspirar medios y añadir 100 µl de Tampón de Lisis Celular de Quinasa IP.

F. Placas de microtitulación de 96 pocillos congelada a -70°C (NOTA: esta etapa se puede hacer durante un mínimo de 1 hora o durante toda una noche.)

Día 3

G. Etapa de placa de 96 pocillos de Proteína de Recubrimiento A/G: añadir concentración apropiada de anticuerpo α-Akt (Akt1, Akt2, o Akt3) en 100 µl de PBS a los siguientes pocillos:

α-Akt 1 (20 ng/pocillo/100ul) B2 >>>>>> B10 / filas B – G / placa Akt1

α-Akt 2 (50 ng/pocillo/100ul) B2 >>>>>> B10 / filas B – G / placa Akt2

IgG de conejo (150 ng/pocillo/100 ul): B11 – G11 en cada placa (Akt1 y Akt2)

H. Incubar en la cámara fría (+4°C) durante 4 horas en el Micromix 5 (Forma 20; Actitud 2) (NOTA: la actitud depende de cual sea la máquina de Micromix 5).

I. Aspirar solución de anticuerpo α-Akt y añadir 100 µl de PBS a cada pocillo.

J. Etapa de Inmunoprecipitación de Akt: a 100 µl de PBS de Etapa (I) añadir 5 µl de lisado de células descongeladas para placas de Akt1 y 10 µl de lisado de células descongeladas para placas de Akt2. NOTA: lisado de células descongeladas en hielo. Lisado fundido de mezcla pipeteando arriba y abajo 10X antes de transferir a placas de anticuerpos. Mantener las placas de lisado celular en hielo. Después de transferencia del lisado celular a las placas de anticuerpos recongelar las placas de lisado celular a -70°C.

K. Incubar en la habitación fría (+4°C) durante toda una noche en agitador de Micromix 5 (forma 20, actitud 3).

Día 4

L. Etapa de Lavado de Placa por Inmunoprecipitación: lavar placas de 96 pocillos 1X con TTBS (RCM 51, 1X = 2 ciclos) usando el Lavador de Placa de 96 Pocillos. Cargar pocillos con TTBS e incubar durante 10 minutos. Lavar placas de 96 pocillos 2X con TTBS. (NOTA: cebar lavador de placa antes de usar: 1). Comprobar los reservorios de tampones, asegurándose de que están llenos y 2. Vaciar contenedores de residuos).

M. Etapa de Lavar Placas Manualmente: añadir 180 µl de tampón de Ensayo de Kinasa IP.

N. Comenzar Reacción de Enzima Akt: aspirar sobrenadante. Añadir 60 µl de solución de sustrato GSK3β.

O. Incubar durante 2,5 horas en agitador Micromix 5 @ RT. NOTA: el tiempo de incubación debería ajustarse tal que la razón de Columna 10/Columna 11 no sea >10.

P. Combinar 30 µl de Tampón de Detección de Lance con 30 µl de Tampón de Parada de Lance (60 µl total/pocillo) y añadir a placas negras de 96 pocillos de fondo en U de Microflúor.

Q. Detener Reacción Enzimática de Akt: transferir 40 µl de Mezcla de Reacción Enzimática de Akt a partir de placa de 96 pocillos de Proteína A/G de Etapa (O) a placas negras de 96 pocillos de fondo en U de Microflúor a partir de la Etapa (P).

U. Incubar a temperatura ambiente durante 1-2 horas en agitador Micromix 5 (forma 20, actitud 3), después leer con el Analizador de Microplaca HTRF de Discovery usando programa de Akt.

310

Tampón de Lisis Celular de Kinasa IP

100 µl por pocillo

| | 8 ml (1 Placa) | | 45 ml (6 Placas) |
|---|---|---|---|
| TBS 1X | 7744 µl | | No disponible |
| Tween 20 | 20 µl | | No disponible |
| Cóctel Inhibidor de Proteasas III 1X | 80 µl | | No disponible |
| Cóctel Inhibidor de Fosfatasa I 1X | | | 450 µl |
| Cóctel Inhibidor de Fosfatasa II 1X | 80 µl | | 450 µl |
| Microcistina LR (500X) | | | 450 µl |
| | 80 µl | | |
| | | | 90 µl |

Tampón de Ensayo de Kinasa IP

100 µl por pocillo

| | 8 ml (1 Placas) | | 50 ml (3 Placas) |
|---|---|---|---|
| Tampón de Ensayo 10X | 800 µl | | 5 ml |
| KCl 1 M | 400 µl | | 2,5 ml |
| ATP 250 mM | 4,8 µl | | 30 µl |
| $MgCl_2$ 1M | 80 µl | | 500 µl |
| Glicerol | 400 µl | | 2,5 ml |
| DTT 1M | 8 µl | | 50 µl |
| Cóctel Inhibidor de Proteasa | 1 comprimido/50 | | 1 |
| BSA al 10% | ml | | 500 µl |
| di $dH_20$ | 80 µl | | 38,9 ml |
| | 6227,2 µl | | |

Solución de Sustrato GSK3ß

60 µl por pocillo

| | 5 ml (1 Placa) | | 7 ml |
|---|---|---|---|
| Tampón de Ensayo de Kinasa IP | 5 ml | | - |
| Péptido GSK3ß 1mM | 2,5 µl | | 3,5 µl |

Tampón de Parada de Lance

30 µl por pocillo

| | 3 ml | 5 ml | 5 ml |
|---|---|---|---|

| | | | |
|---|---|---|---|
| | (1 Placa) | | |
| Tampón de Lance 1X<br>EDTA 0,5 M | 2800,2 µl<br>199,8 µl | | |

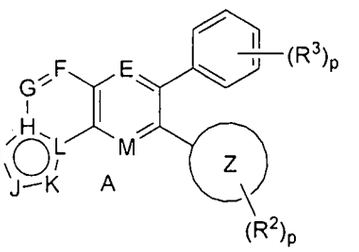
Tampón de Detección de Lance

30 µl por pocillo

| | 3 ml<br>(1 Placa) | | 5 ml |
|---|---|---|---|
| SA-APC (1 mg/ml en ddH2O, diluir 1/75,2 en Tampón de Lance)<br>EuK Ab a-fosfo (Ser 21)GSK3ß (680 nM, diluir 1/1133 en Tampón de Lance) | 40 µl<br>2,7 µl | | 66,7 µl<br>4,5 µl |

## REIVINDICACIONES

1. Un compuesto de acuerdo con la Fórmula A:




en la que:

E, F, G, H, I, J, K, L y M se seleccionan independientemente de: C o N, en la que cada E, F, G, H, I, J, K, L y M está opcionalmente sustituido con $R^1$;

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2; p es independientemente 0, 1, 2, 3, 4 ó 5;

El anillo Z se selecciona de: cicloalquilo($C_3$-$C_8$), arilo, heteroarilo y heterociclilo;

$R^1$ se selecciona de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^2$ se selecciona independientemente de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), SH, $S(O)_mNR^7R^8$, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^3$ se selecciona independientemente de: oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquilo($C_1$-$C_6$)-heterociclilo y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^6$ es: $(C=O)_aO_b$alquilo $C_1$-$C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2$-$C_{10}$, alquinilo $C_2$-$C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1$-$C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) o $(C=O)_aO_b$cicloalquilo $C_3$-$C_8$, dichos alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O_a$perfluoroalquilo($C_1$-$C_3$), alquileno($C_0$-$C_6$)-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), cicloalquilo($C_3$-$C_6$), alquileno($C_0$-$C_6$)-arilo, alquileno($C_0$-$C_6$)-heterociclilo, alquileno($C_0$-$C_6$)-$N(R^b)_2$, $C(O)R^a$, alquileno($C_0$-$C_6$)-$CO_2R^a$, C(O)H, y alquileno($C_0$-$C_6$)-$CO_2H$, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$;

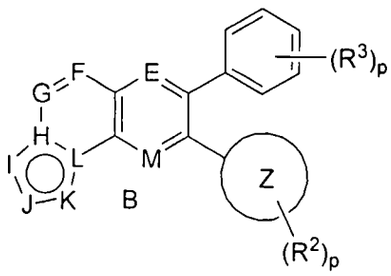
$R^7$ y $R^8$ están independientemente seleccionados de: H, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), SH, $SO_2R^a$, y $(C=O)_aNR^b{}_2$, dichos alquilo, cicloalquilo, arilo, heterociclilo, alquenilo, y alquinilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y que opcionalmente contienen, además del nitrógeno, uno o dos heteroátomos adicionales seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^a$ es alquilo($C_1$-$C_6$), cicloalquilo($C_3$-$C_6$), arilo, o heterociclilo; y

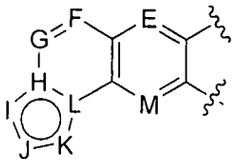
$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), alquilo$(C=O)_aO_b$($C_1$-$C_6$), o $S(O)_mR^a$;

o una sal farmacéuticamente aceptable o un estereoisómero del mismo.

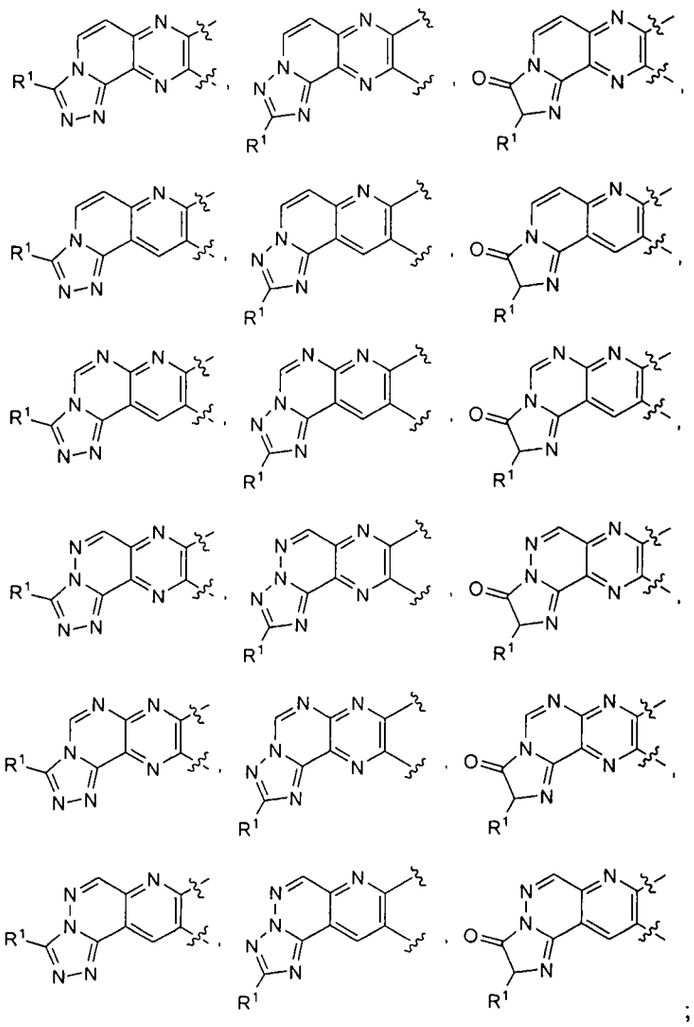
2. Un compuesto de acuerdo con la Fórmula B:




en la que:




se selecciona de:

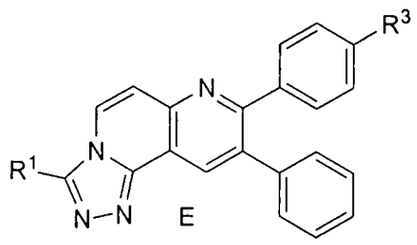


;

$R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

y todos los otros sustituyentes y variables como se definen en la reivindicación 1;
o una sal farmacéuticamente aceptable o un estereoisómero del mismo.

3. Un compuesto de acuerdo con la Fórmula E:



E

en la que:

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2;

$R^1$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^3$ se selecciona de: H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquilo($C_1$-$C_6$)-heterociclilo y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterocicliclo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^6$;

$R^6$ es: $(C=O)_aO_b$alquilo $C_1$-$C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2$-$C_{10}$, alquinilo $C_2$-$C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1$-$C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) o $(C=O)_aO_b$cicloalquilo $C_3$-$C_8$, dichos alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O_a$perfluoroalquilo($C_1$-$C_3$), alquileno($C_0$-$C_6$)-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), cicloalquilo($C_3$-$C_6$), alquileno($C_0$-$C_6$)-arilo, alquileno($C_0$-$C_6$)-heterociclilo, alquileno($C_0$-$C_6$)-$N(R^b)_2$, $C(O)R^a$, alquileno($C_0$-$C_6$)-$CO_2R^a$, C(O)H, y alquileno($C_0$-$C_6$)-$CO_2H$, dichos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, y heterocicliclo están opcionalmente sustituidos con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$;

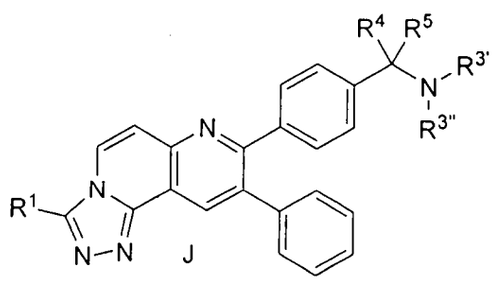
$R^7$ y $R^8$ están independientemente seleccionados de: H, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), SH, $SO_2R^a$, y $(C=O)_aNR^b{}_2$, dichos alquilo, cicloalquilo, arilo, heterociclilo, alquenilo, y alquinilo están opcionalmente sustituidos con uno o más sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y que opcionalmente contienen, además del nitrógeno, uno o dos heteroátomos adicionales seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituido con uno o más sustituyentes seleccionados de $R^{6a}$;

$R^a$ es alquilo($C_1$-$C_6$), cicloalquilo($C_3$-$C_6$), arilo, o heterociclilo; y

$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), alquilo$(C=O)_aO_b$($C_1$-$C_6$), o $S(O)_mR^a$;

o una sal farmacéuticamente aceptable o un estereoisómero del mismo.

4. Un compuesto de acuerdo con la Fórmula J:




J

en la que:

a es 0 ó 1; b es 0 ó 1; m es 0, 1 ó 2;

$R^1$ se selecciona de: $CF_3$, H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH, $O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterociclilo están opcionalmente sustituidos con de uno a seis sustituyentes seleccionados de $R^6$;

$R^{3'}$ y $R^{3''}$ se selecciona independientemente de: $CF_3$, H, oxo, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$alquenilo($C_2$-$C_{10}$), $(C=O)_aO_b$alquinilo($C_2$-$C_{10}$), $CO_2H$, halo, OH,

$O_b$perfluoroalquilo($C_1$-$C_6$), $(C=O)_aNR^7R^8$, CN, $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$), alquil($C_1$-$C_6$)-heterociclilo y $(C=O)_aO_b$-heterociclilo, dichos alquilo, arilo, alquenilo, alquinilo, cicloalquilo, y heterociclilo están opcionalmente sustituidos con uno a cinco sustituyentes seleccionados de $R^6$; o $R^{3'}$ y $R^{3''}$ se pueden tomar conjuntamente con el nitrógeno al cual están anclados para formar una piperidina o pirrolidina la cual puede estar opcionalmente sustituida con de uno a cinco sustituyentes seleccionados de $R^6$;

$R^4$ y $R^5$ son independientemente: H, alquilo($C_1$-$C_6$), alquenilo($C_1$-$C_6$), alquinilo($C_1$-$C_6$), en el que dicho alquilo está opcionalmente sustituido con de uno a tres sustituyentes seleccionados de: OH y halo; y en los que $R^4$ y $R^5$ se pueden tomar conjuntamente para formar un cicloalquilo($C_3$-$C_7$), en el que dicho cicloalquilo está opcionalmente sustituido con hasta tres sustituyentes seleccionados de $R^6$;

$R^6$ es: $CF_3$, $(C=O)_aO_b$alquilo $C_1$-$C_{10}$, $(C=O)_aO_b$arilo, alquenilo $C_2$-$C_{10}$, alquinilo $C_2$-$C_{10}$, $(C=O)_aO_b$ heterociclilo, $CO_2H$, halo, CN, OH, $O_b$perfluoroalquilo $C_1$-$C_6$, $O_a(C=O)_bNR^7R^8$, oxo, CHO, $(N=O)R^7R^8$, $S(O)_mNR^7R^8$, SH, $S(O)_m$-alquilo($C_1$-$C_{10}$) o $(C=O)_aO_b$cicloalquilo $C_3$-$C_8$, dicho alquilo, arilo, alquenilo, alquinilo, heterociclilo, y cicloalquilo opcionalmente sustituido con de uno a cinco sustituyentes seleccionados de $R^{6a}$;

$R^{6a}$ se selecciona de: $CF_3$, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $O_a$perfluoroalquilo($C_1$-$C_3$), alquileno($C_0$-$C_6$)-$S(O)_mR^a$, SH, oxo, OH, halo, CN, alquenilo ($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), cicloalquilo($C_3$-$C_6$), alquileno($C_0$-$C_6$)-arilo, alquileno($C_0$-$C_6$)-heterociclilo, aquileno($C_0$-$C_6$)-$N(R^b)_2$, $(C=O)_aNR^b_2$, $C(O)R^a$, alquileno($C_0$-$C_6$)-$CO_2R^a$, C(O)H, y alquileno($C_0$-$C_6$)-$CO_2H$, dichos alquilo, alquenilo, alquinilo, cicloalquilo, arilo, y heterociclilo está opcionalmente sustituido con hasta tres sustituyentes seleccionados de $R^b$, OH, alcoxi($C_1$-$C_6$), halógeno, $CO_2H$, CN, $O_a(C=O)_b$alquilo($C_1$-$C_6$), oxo, y $N(R^b)_2$;

$R^7$ y $R^8$ están independientemente se seleccionados de: $CF_3$, H, $(C=O)_aO_b$alquilo($C_1$-$C_{10}$), $(C=O)_aO_b$cicloalquilo($C_3$-$C_8$), $(C=O)_aO_b$-arilo, $(C=O)_aO_b$-heterociclilo, alquenilo($C_2$-$C_{10}$), alquinilo($C_2$-$C_{10}$), SH, $SO_2R^a$, y $(C=O)_aNR^b_2$, dichos alquilo, cicloalquilo, arilo, heterocililo, alquenilo, y alquinilo están opcionalmente sustituidos con de uno a cinco sustituyentes seleccionados de $R^{6a}$, o $R^7$ y $R^8$ se pueden tomar conjuntamente con el nitrógeno al cual se han anclado para formar un heterociclo monocíclico o bicíclico con 3-7 miembros en cada anillo y conteniendo opcionalmente, además del nitrógeno, uno o dos heteroátomos adicionales seleccionados de N, O y S, dicho heterociclo monocíclico o bicíclico opcionalmente sustituido con de uno a seis sustituyentes, seleccionados de $R^{6a}$;

$R^a$ es alquilo ($C_1$-$C_6$), $NR^b_2$, cicloalquilo ($C_3$-$C_6$), arilo, o heterociclilo; y

$R^b$ es independientemente: H, alquilo($C_1$-$C_6$), $NH_2$, arilo, heterociclilo, cicloalquilo($C_3$-$C_6$), $(C=O)_aO_b$alquilo($C_1$-$C_6$), o $S(O)_mR^a$;

o una sal farmacéuticamente aceptable o un estereoisómero del mismo.

5. Un compuesto el cual se selecciona de:

[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-il]metilcarbamato de *terc*-butilo

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-ol;

9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-amina;

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-tiol;

3-metil-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(clorometil)-9-fenil-8-(4-{[4-(4-piridin-2-il-1H-imidazol-1-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-[(4-metilpiperazin-1-il)metil]-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

2-({[9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metil}amino)etanol;

8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-3-ol;

1-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*][1,6]naftiridin-8-il)-bencilamina;

8-[4-(aminometil)-fenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-amina;

1-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina;

9-fenil-8-{4-{[4-(5-piridin-2-il-4*H*-1,2,4-triazol-3-il)-piperidin-1-il]metil}fenil}-[1,2,4]triazolo[3,4-*f*][1,6]naftiridina;

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina;

320

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina-3-il]metilcarbamato de *terc*-butilo;

[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol;

5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]-2,4-dihidro-3H-1,2,4-triazol-3-ona;

3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4] triazolo[3,4-f]-1,6-naftiridina;

3-imidazo[1,2-a]piridin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina;

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,4-triazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(1H-benzimidazol-6-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil) [1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil} fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-imidazo[1,2-a]pirimidin-2-il-9-fenil-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

5-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina;

9-fenil-3-pirazolo[1,5-a]pirimidin-3-il-8-(4-{[4-(5-piridin-2-il-1H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(5-metil-1H-pirazol-3-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]piridin-2-amina;

4-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol;

3-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol;

2-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]fenol;

1-{4-[3-(5-oxo-4,5-dihidro-1H-1,2,4-triazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida;

1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]piperidina-4-carboxamida;

9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

9-fenil-8-(4-{[4-(5-pirimidin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

3-(1-metil-1H-imidazol-4-il)-9-fenil-8-(4-{[4-(5-pirazin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;

N-[2-(4-metil-1H-imidazol-2-il)etil]-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}amina;

$N^1$-(2-hidroxifenil)-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-beta-alaninamida;

1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida;

5-[({4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}amino)metil]piridin-2-ol;

$N^1$,$N^1$,2,2-tetrametil-$N^3$-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il] bencil}propano-1,3-diamina;

3-hidroxi-2,2-dimetil-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

2-fluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

2,2-difluoro-3-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

2,3-dihidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]ciclohexanamina;

4-hidroxi-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]ciclohexanamina;

3-hidroxi-2,2-dimetil-N-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}propan-1-amina;

3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

3-hidroxi-2,2-dimetil-N-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

3-hidroxi-2,2-dimetil-N-{4-(9-fenil-3-(1H-1,2,3-triazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]propan-1-amina;

{[8-(4-{[(3-hidroxi-2,2-dimetilpropil)amino]metil}fenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metil}carbamato de *terc*-butilo;

N-{4-[3-(amoniometil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-3-hidroxi-2,2-dimetilpropan-1-amina;

[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol;

$N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(2-hidroxifenil)-beta-alaninamida;

(8-{4-[(ciclohexilamino)metil]fenil}-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il)metanol;

$N^3$-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}-$N^1$-(4-hidroxifenil)-beta-alaninamida;

[9-fenil-8-(4-{[4-(5-piridin-3-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanol;

1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencil}piperidina-4-carboxamida;

{8-[4-(1-aminociclopropil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol;

1-[4-(9-fenil-3-piridin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

1-{4-[3-(1-oxidopiridin-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-[4-(3,9-difenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

1-{4-[3-(4-fluorofenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

4-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}benzonitrilo;

4-(9-fenil-3-piridin-4-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina;

1-{4-[3-(1-oxidopiridin-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

5-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}iridina-2-ol;

1-[4-(9-fenil-3-piridin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencilamina,

1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

1-[4-(9-fenil-3-pirazin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

1-{4-[9-fenil-3-(1H-1,2,4-triazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-[4-(9-fenil-3-(1H-pirazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

1-{4-[3-(3-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[3-(3-metil-1H-1,2,4-triazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[3-(1-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[9-fenil-3-(1,2,5-tiadiazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[9-fenil-3-(1,2,3-tiadiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil}metanamina;
{8-[4-(aminometil)-fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanamina;
{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metanol;
1-{4-[9-fenil-3-(2,2,2-trifluoroetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
1-[4-(9-fenil-3-(1H-tetraazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
8-(4-aminometil-fenil)-9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-carboxamida;
1-{4-[3-(acetidin-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[4-(3-metilsulfonil)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}acetonitrilo;
2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol;
N-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)acetamida;
4-[3-(2-metilimidazo[1,2-a]piridin-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;
1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-3-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
1-[4-(3-imidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1,2-benzisoxazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina;
1-{4-[3-(1-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
4-[3-(1-metil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}bencilamina;
1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1-benzotien-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[3-(1-isopropil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[9-fenil-3-(1,4,5,6-tetrahidrociclopenta[c]pirazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[4-(9-fenil-3-[(2S)-pirrolidin-2-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
4-[3-(1-aminoetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;
1-{4-[3-(1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[4-(3-ciclopropil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
1-[4-(9-fenil-3-(trifluorometil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[3-(5-metil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
4-[3-(1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}bencilamina;
1-{4-[3-(1-metil-1H-imidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[3-(3-metil-2H-3lamda$^5$-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

4-[3-(6-cloroimidazo[1,2-a]piridin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;

1-{4-[3-(1H-bencimidazol-2-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

4-[3-(5-ciclopropil-4H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;

1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-1H-indazol-3-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina

4-[9-fenil-3-(3-fenil-1H-pirazol-5-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;

1-(4-{9-fenil-3-[3-(trifluorometil)-1H-pirazol-5-il][1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina;

1-[4-(9-fenil-3-pirazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

1-{4-[3-(1-bencil-1H-pirazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;

4-[9-fenil-3-(1-fenil-H-pirazol-4-ii)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]bencilamina;

1-{4-[9-fenil-3-(4,5,6,7-tetrahidro-2-benzotien-1-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[9-fenil-3-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-2-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}propan-2-amina;

1-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etano-1,2-diol;

4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}imidazolidin-2-ona;

(2R)-2-amino-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}etanol;

(2R)-2-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2-(metilamino)etanol;

1-{4-[3-(5-etilisoxazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

5-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-2,4-dihidro-3H-1,2,4-triazol-3-ona;

6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-4,5-dihidropiridazin-3(2H)-ona;

6-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}piridazin-3(2H)-ona;

N-[({4-[8-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)acetamida;

1-{4-[3-(4-fenoxifenil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

1-{4-[3-(1H-bencimidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;

(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}fenil)metanol;

4-[3-(4-ciclohexilfenil)-9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;

(4-{8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}-1,3-dihidro-2H-imidazol-2-ona;

1-{4-[3-(1-metil-1H-imidazol-5-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[9-fenil-3-(1-propil-1H-imidazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]bencilamina;
1-{4-[3-(1-isopropil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[3-(1-butil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-[4-(3-imidazo[1,2-a]pirimidin-2-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
5-({[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amino}metil)piridin-2-ol;
1-(6-metoxipiridin-3-il)-N-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]metanamina;
N-[(2-metoxipirimidin-5-il)metil]-N-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amina;
1-[4-(3-etil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
1-[4-(9-fenil-3-propil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]metanamina;
N-[4-(9-fenil-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]acetamida;
4-({[4-(9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amino}metil)fenol;
1-[9-fenil-8-(4-{[4-(5-piridin-2-il-4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il]metanamina;
9-fenil-3-(1H-1,2,3-triazol-4-il)-8-(4-{[4-(4H-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-f]-1,6-naftiridina;
1-{4-[3-(1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[9-fenil-3-(3H-1lamda$^4$,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[9-fenil-3-(1H-pirazol-3-il)-2H-4lambda$^5$-[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-{4-[9-fenil-3-(1,3-tiazol-4-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
4-[9-fenil-3-(piperazin-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;
1-{4-[3-(acetidin-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
1-({8-[4-(aminometil) fenil]-9-fenil[1,2,4] triazolo[3,4-f]-1,6-naftiridin-3-il} metil)piperidina-4-carboxamida;
1-{4-[3-(morfolin-4-ilmetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}metanamina;
2-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)amino]etanol;
1-(4-{3-[(4-metil piperazin-1-il)metil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il}fenil)metanamina;
4-[9-fenil-3-(piperazin-1-ilmetil)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]bencilamina;
N-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)-N-metilamina;
N-[({8-[4-(aminometil)fenil]-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-3-il}metil)-N,N-dimetilamina;
[4-(3-metil-9-fenil-[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]metanol;
{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}metanol;
1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*]pirimidin-2-il[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanol;
9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
3-metil-9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;

9-fenil-8-(4-{[4-(4*H*-1,2,4-triazol-3-il)piperidin-1-il]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-3-ol;
1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropanamina;
1-{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}ciclopropanamina;
1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-*a*]pirimidin-2-il[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropanamina;
1-{4-[9-fenil-3-(5,6,7,8-tetrahidroimidazo[1,2-a]piridin-2-il)[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}ciclopropanamina;
1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]ciclopropanamina;
1-{4-[3-(1,5-dimetil-1H-pirazol-3-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}ciclopropanamina;
(1R)-1-{4-[3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina;
(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etanamina;
(1*R*)-1-{4-[9-fenil-3-(5-piridin-2-il-1*H*-pirazol-3-il)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il]fenil}etanamina;
(1R)-1-{4-[3-(hidroximetil)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina;
(1R)-1-{4-[3-(1-metil-1H-imidazol-4-il)-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il]fenil}etanamina;
(1R)-1-[4-(9-fenil-3-[1,2,4]triazolo[1,5-a]pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina;
(1R)-1-[4-(3-imidazo[2,1-b][1,3]tiazol-6-il-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina;
(1R)-1-[4-(9-fenil-3-pirimidin-2-il[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)fenil]etanamina;
(1*R*)-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-1-amina;
2-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina;
2-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]propan-2-amina;
3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-oxoetil)piridina;
*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-4-il-2-furamida;
*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-2-furamida;
*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]-5-piridin-3-il-1*H*-pirrolo-3-carboxamida;
2-hidroxi-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida;
(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]amino}-2-oxoetil)carbamato de *terc*-butilo;
4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)morfolina;
2-({[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-f]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetanamina;
4-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina;

2,4-dihidroxi-6-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)pirimidina;

2-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)piridina;

3-(2-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-oxoetil)piridina;

*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-pirazin-2-ilacetamida;

3-metil-9-fenil-8-[4-({[(piridin-3-ilamino) carbonil]amino}metil)fenil][1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;

2-(2-hidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;

2-(3-hidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;

2-(4-hidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;

2-(3,4-dihidroxifenil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;

*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-fenilacetamida;

3-metil-9-fenil-8-[4-({[(piridin-3-ilcarbonil]amino}metil)fenil][1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;

2-hidroxi-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]benzamida;

2-(4-hidroxifenil)-2-metil-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]propanamida;

4-{[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-4-oxobutanoato de metilo;

2-hidroxi-*N*-(2-{[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]amino}-2-oxoetil)benzamida;

*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil] -2-(5-fenil-4*H*-1,2,4-triazol-3-il)acetamida;

3-metil-9-fenil-8-[4-({[(piridin-3-ilcarbonil]amino}metil)fenil][1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;

*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-(4-oxoquinazolin-3(4*H*)-il)acetamida;

*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]-2-(2-oxo-1,3-benzoxazol-3(2*H*)-il)acetamida;

8-(4-{[(1*H*-benzimidazol-1-ilacetil)amino]metil} fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;

8-(4-{[(1*H*-benzimidazol-2-ilacetil)amino]metil} fenil)-3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;

2-(4-metil-1,2,5-oxadiazol-3-il)-*N*-[4-(3-metil-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il) bencil]acetamida;

2-(1*H*-indazol-1-il)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;

2-(5,6-dimetil-4-oxotieno[2,3-*d*]pirimidin-3(4*H*)-il)-*N*-[4-(3-metil-9-fenil [1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;

3-metil-8-[4-({[(6-morfolin-4-ilpiridin-3-il)carbonil]amino}metil)fenil]-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridina;

2-(6-cloropiridin-3-il)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;
3-ciano-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]propanamida;
3-metil-9-fenil-8-(4-{[(3-piridin-3-ilpropanoil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{[(piridin-3-ilacetil)amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
9-fenil-3-pirazolo[1,5-*a*]pirimidin-3-il-8-(4-{[(piridin-3-ilacetil) amino]metil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
*N*-(3-hidroxi-2,2-dimetilpropil)-*N*-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil]acetamida;
*N*-(3-hidroxi-2,2-dimetilpropil)-*N*-{4-[3-(1-metil-1*H*-imidazol-4-il)-9-fenil[1,2,4] triazolo[3,4-*f*]-1,6-naftiridin-8-il] bencil}-2-(4-oxoquinazolin-3(4*H*)-il)acetamida;
{2-[[4-(3-{[(*terc*-butoxicarbonil) amino]metil}-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)bencil](3-hidroxi-2,2-dimetilpropil)amino]-2-oxoetil}carbamato de *terc*-butilo;
3-metil-9-fenil-8-(4-{1-[(piridin-3-ilacetil]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
3-metil-9-fenil-8-(4-{1-[(quinolin-3-ilcarbonil]amino}ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
*N*-{1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]ciclopropil}-2-(4-oxoquinazolin-3(4*H*)-il)acetamida;
3-(1-metil-1*H*-imidazol-4-il)-9-fenil-8-(4-{[(piridin-3-ilacetil)amino]ciclopropil}fenil)[1,2,4]triazolo[3,4-*f*]-1,6-naftiridina;
*N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}-2-piridin-3-ilacetamida;
*N*-{(1*R*)-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}acetamida;
*N*-((1*R*)-1-{4-(3-hidroximetil)-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}-2-piridin-3-ilacetamida;
*N*-{1-metil-1-[4-(9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il) fenil]etil}acetamida; y
*N*-{1-metil-1-[4-(3-metil-9-fenil[1,2,4]triazolo[3,4-*f*]-1,6-naftiridin-8-il)fenil]etil}acetamida;

o una sal farmacéuticamente aceptable o estereoisómero del mismo.

6. Una composición farmacéutica que comprende un transportador farmacéutico, y dispersa en él, una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1.

7. El uso de un compuesto de acuerdo con la reivindicación 1 para la preparación de un medicamento útil en el tratamiento o prevención de cáncer en un mamífero en necesidad de tal tratamiento.

330

RESUMEN DE LA DESCRIPCIÓN

La invención actual estipula compuestos de naftiridina sustituidos que inhiben actividad Akt. En particular, los compuestos descritos inhiben selectivamente una o dos de las isoformas de Akt. La invención también estipula composiciones que comprenden tales compuestos inhibidores y procedimientos para inhibir actividad Akt administrando el compuesto a un paciente en necesidad de tratamiento de cáncer.

LISTADO DE SECUENCIAS

331

<110> Merck & Co., Inc.
Armstrong, Donna
Kelly III, Michael J.
Layton, Mark
Liang, Jun
Li, Yiwei
Hu, Essa H.
Rodzinak, Kevin
Rossi, Mike
Sanderson, Phil
Wang, Jiabing

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<220>
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<220>
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<210> 12
<211> 30
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<210> 13
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<210> 14
<211> 6

334

<212> PRT
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<220>
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<400> 14
Glu Tyr Met Pro Met Glu
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<210> 15
<211> 13
<212> PRT
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<210> 16
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<220>
<223> Secuencia Aminoacídica Completamente Sintética

<400> 16
Lys Lys Gly Gly Arg Ala Arg Thr Ser Ser Phe Ala Glu Pro Gly
1 5 10 15

335

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-129906- -00000-0000

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SUPERINTENDENCIA

# REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Felipe Novoa

Firma Responsable

Fecha 07-12-07

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia